SYSTEMATIC REVIEW

Systemic Treatment for Metastatic Hormone Sensitive Prostate Cancer: A Comprehensive Meta-Analysis Evaluating Efficacy and Safety in Specific Sub-Groups of Patients

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Abstract

Background and Objectives Several systemic treatments are available for metastatic hormone sensitive prostate cancer (mHSPC) including docetaxel (D), abiraterone and prednisone (A + P) and new anti-androgens (NA). In our study we performed a systematic review and meta-analysis assessing efficacy outcomes (survival and radiological-free survival), safety and survival on specific subgroups of patients.

Methods Outcomes of interest were: (i) Risk of death, biochemical and radiological progression among all patients. (ii) Risk of death according to different pathological/clinical features. (iii) Evaluation of the relative risk (RR) and risk difference of serious toxicity defined as adverse events (AEs) with grade ≥ 3 specific AEs. Hazard ratios (HRs) and RR were measures adopted for endpoints 1–3.

Results Overall, eight randomized trials were included in meta-analysis for a total of 9987 patients. Administration of D, A + P and NA resulted in improved overall survival (OS) and radiological progression-free survival (rPFS). Survival benefit was not confirmed in patients receiving NA and previously exposed to docetaxel (HR 0.948, 95% CI 0.671–1.338). Patients with visceral metastases and high lactate dehydrogenase (LDH) did not benefit from NA treatment, while it seems that patients with low Gleason score do not benefit from A + P. NA showed the more favorable safety profile.

Conclusion NA may not provide survival benefit when adopted subsequently or in concomitant to D. Specific subgroups of patients may benefit more from A + P, D or NA. Safety profiles significantly differ among agents evaluated.

1 Introduction

Prostate cancer (PC) is the most common malignancy in men representing about 20% of oncological diagnosis [1]. Among this large group, only 3%–4% of patients present a

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metastatic hormone sensitive prostate cancer (mHSPC) as primary diagnosis [2].

Compared to patients developing metastasis after curative treatment, de-novo mHSPC is a disease correlated with worst prognosis and shorter time to develop a metastatic castration-resistant prostate cancer (mCRPC) [3].

Nonetheless, there are specific subgroups of patients with mHSPC who presented more favorable prognosis. Generally, these patients present low tumor burden, small metastatic disease and low Gleason [4].

Traditionally, systemic management of mHSPC has been carried out through an androgen deprivation therapy (ADT). However, in recent years, several trials evaluating the addition of systemic compounds to ADT showed that combination treatment results in improved clinical outcomes. Docetaxel was the first systemic agent tested in this setting [5–9], followed by abiraterone–prednisone [10, 11]. Very recently, data from randomized studies demonstrated that the administration of new anti-androgen compounds with

△ Adis

Key Points

Several drugs have shown clinical efficacy in patients with mHSPC.

Efficacy of these agents may be significantly different according to pathological and clinical variables.

Safety profiles of each drug are significantly different.

ADT resulted in a survival and clinical advantage in patients with mHSPC [12–14].

To date, two different studies performed a comparison between these agents.

Marchioni et al performed a network meta-analysis showing that administration of new anti-androgen compounds with ADT does not reflect a survival advantage compared to docetaxel [15]. However, administration of hormonal compounds is associated with lower disease progression rates and better safety profile [16]. Similarly, Sathianathen et al performed a systematic review and network meta-analyses to characterize the comparative efficacy of combination treatments in patients with mHSPC [16]. Combination therapies between ADT and other compounds (both chemotherapy or hormonal agents) can improve patients' prognosis and overall survival [16].

Here, we carried out a meta-analysis aimed to assess the toxicity profiles of these treatments, the survival and progression-free survival (PFS) benefit in all patients and the survival benefit in patients with specific clinical/pathological behaviors.

2 Methods

2.1 Evidences Acquisition

This meta-analysis has been carried out according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.

2.2 Search Strategies

We searched all perspective, randomized Phase III clinical trials published between 01 January 2012 to 15 September 2019 evaluating a new hormonal agent or other compounds in addition to ADT in patients with mHSPC.

Keywords used for searching on Pubmed/Medline, Cochrane library, and Scopus, were: "*metastatic hormone sensitive prostate cancer*" OR "*mHSPC*" OR "*metastatic prostate cancer*" OR "*Castration sensitive metastatic prostate cancer*" AND "*apalutamide*" OR "*enzalutamide*" OR

"*abiraterone*" OR "*docetaxel*"; only papers published in peer-reviewed journals, and written in English language, were considered. Furthermore, proceedings of the main International Oncological and Urological meetings (American Society of Clinical Oncology, European Society of Medical Oncology, American Association for Cancer Research, European Association of Urology, and American Urological Association) were also evaluated for relevant abstracts. When more publications of the same study were available, we adopted the more recent publication with longer follow up. Four authors (VDN, FM, VM and MS) made a first study selection. Therefore, all authors reviewed all relevant studies selected before their inclusion in analyses.

2.3 Aims of the Meta-Analysis

Aims of the meta-analysis were:

(i) To evaluate risk of death, biochemical and radiological progression-free survival (bPFS and rPFS) among patients with mHSPC randomized to ADT or ADT + experimental compound. For this aim, only studies reporting completed results of overall survival (OS), bPFS and rPFS analyses were evaluated. Our aim was to evaluate the different risks of death bPFS and rPFS in previously untreated and treated patients with mHSPC.

(ii) To evaluate risk of death of specific patient subpopulations randomized to ADT or ADT + experimental compound. Variables of interest were: ECOG performance status (0 vs 1–2), age ($< 70, \geq 70$), visceral metastases (yes/no), Gleason ($< 8, \geq 8$), lactate dehydrogenase (LDH) levels (high/normal), high volume disease (yes/no). For this aim, only studies reporting completed survival outcomes in these subgroups as well as studies reporting bPFS analysis were considered.

(iii) To evaluate the relative risk (RR) and risk difference of serious toxicity defined as adverse events (AEs) with grade ≥ 3 of specific AEs such as: fatigue, falls, seizure/dizziness, cardiovascular toxicity, death due to AE, hypertension, neutropenia, febrile neutropenia, anemia, thrombocytopenia, arthralgia and edema.

2.4 Data Extraction and Synthesis

The following data were extracted for each publication: (a) population on study (b) OS expressed as hazard ratio (HR) with 95% confidence interval (CI); (c) rPFS expressed as HR with 95% CI, (d) bPFS expressed as HR with 95% CI; (d) OS expressed as HR in patients with ECOG performance status 0, ECOG performance status 1, age < 70, age ≥ 70, absence

of visceral metastases, presence of visceral metastases, high volume disease, Gleason score < 8 and Gleason score of 8 or more (g) serious AEs (fatigue, falls, seizure/dizziness, cardiovascular toxicity, death due to AE, hypertension, neutropenia, febrile neutropenia, anemia, thrombocytopenia, arthralgia and edema) with Grade 3 or more occurred among trials considered; (h) median follow up; (h) primary and secondary endpoints of trials exanimated.

Four separate authors (VDN, VM, MS and FM) independently conducted the search and identification at four different times. Results of the research were then shared among all authors before final inclusion in analysis. The same process was adopted for quantifying the risk of bias according to Cochrane tool for risk of bias assessment in randomized trials [17]. Evaluation of studies according to Cochrane tool for risk of bias was performed considering the presence of: (1) selection bias (presence/absence of bias due to inadequate generation of a randomized sequence or inadequate concealment of allocations before assignment); (2) performance bias (knowledge of the allocated interventions by participants and personnel during study); (3) detection bias (knowledge of the allocated interventions by outcome assessment); (4) attrition bias (presence of incomplete outcome data); (5) reporting bias (selective outcome reporting); (6) other bias.

2.5 Statistical Design

Endpoints of the meta-analysis: the evaluation of risk of death, risk of bPFS and rPFS all patients (endpoint 1), the different risk of death in specific subgroups (endpoint 2). Furthermore, we performed a safety analysis among clinical trials evaluating the pooled RR of each specific toxicity of interest (endpoint 3). Meta-analysis was performed using the MedCalc (ver 18.11.3); Excel was used for data collection.

Endpoint 1, 2: Summary measures were HRs with 95% CIs for rPFS, bPFS and OS. We applied the inverse variance technique for the meta-analysis of HRs. In OS/rPFS analyses, we adopted both a random and a fixed-effects model. Statistical heterogeneity between studies was examined using I^2 statistic [17–22].

Endpoint 3: The number of patients receiving experimental drugs, as well as the number of grade 3 or higher AEs in both treatment and control arms were extracted from all selected studies. Incidences, RR and 95% CIs were subsequently calculated as proposed by Altman et al [8]. Cochran's Q statistic was employed to test heterogeneity between studies. The I^2 statistic was chosen for quantification of inconsistency. Both the inverse variance fixed-effects model (weighted with inverse variance) and the random effect model was adopted. Studies with no AE in the treatment or control arms were corrected according to Yates.

Risk difference was estimated as the difference between experimental and comparator arm, which was then expressed as percentage [17–22].

3 Results

3.1 Studies Selection

We selected ten publications [5–14] of the 2892 detected as potentially relevant studies. The main reasons for exclusion: other setting of intervention, review articles, not randomized clinical trials, letters, systematic review or meta-analysis (Fig. 1; Supplementary Material). At the end of the process, eight randomized clinical trials were selected.

In Table 1 we summarized the design of the study, patients enrolled, primary and secondary endpoints. Among the studies included, two were upgraded versions of previous published studies [6, 8]. One randomized trial was presented during an international meeting but lacked mature data on OS [14]. On the basis of the independent evaluation, seven studies were associated with low risk of bias. One study presented a moderate risk of bias mainly due to the immature follow up. Five of the eight studies selected were associated with high risk of bias in the blinding of outcomes and assessment section. This was mainly due to the lack of placebo/double-blind control. Additionally, one of these studies presented an uncertain risk of bias due to the absence of complete data about safety analyses [7, 8]. Overall, 9987 patients were included in this meta-analysis. Of these, 4994 patients received ADT monotherapy, while 4993 received ADT plus experimental compounds. In particular, among 4993 patients included in experimental arms, 1774 received docetaxel (593 also received zoledronic acid), 1557 received abiraterone, 1662 were treated with enzalutamide ($n = 1137$) and apalutamide ($n = 525$).

Of note, in the STAMPEDE trials, we considered only patients with metastatic disease for bPFS, rPFS, OS and subgroup analyses (Table 2).

3.2 Overall Survival (OS) and Radiological Progression-Free Survival (rPFS) Analysis

Seven of eight [5–13] studies were considered for OS analysis (1 study excluded as OS follow up was still immature [14]).

Overall, the administration of experimental compounds resulted in a survival advantage (pooled-random HR 0.714; CI 0.656–0.777; p value < 0.001; $I^2 = 15.66\%$, $p = 0.31$; Fig. 2a.1). The survival advantage was confirmed after the inclusion of previously untreated patients (pooled-random HR 0.697; CI 0.629–0.772; p value < 0.001; $I^2 = 37.78\%$, $p = 0.13$; Fig. 2a.2) and previous docetaxel or concomitant

Fig. 1 Study selected for meta-analysis
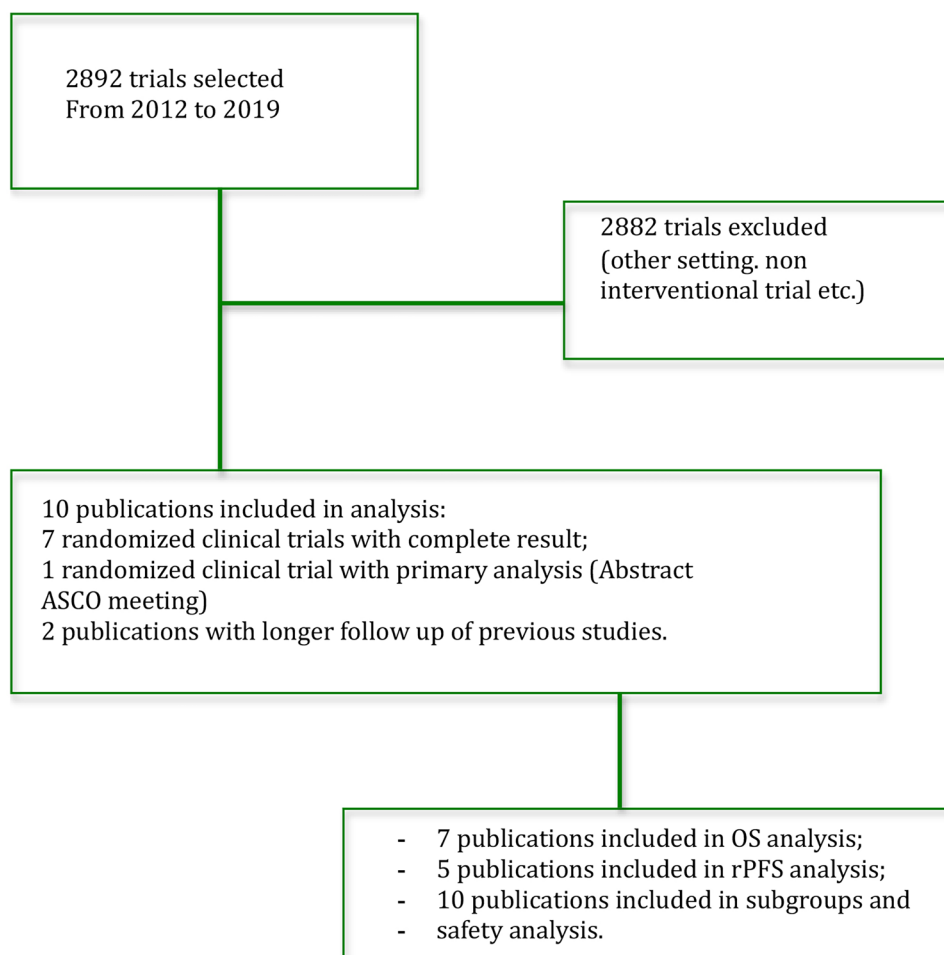
exposed patients (pooled-random HR 0.736; CI 0.662–0.819; p value < 0.001; $I^2 = 35.59\%$, $p = 0.14$; Fig. 2a.3).

Survival benefit was demonstrated in patients treated with docetaxel (pooled-random HR 0.736; CI 0.662–0.819; p value < 0.001; $I^2 = 0.00\%$, $p = 0.69$; Fig. 2c.1), abiraterone (pooled-random HR 0.615, 95% CI 0.532–0.712; p value < 0.001; $I^2 = 0.00\%$, $p = 0.91$; Fig. 2c.2) and new anti-androgens (pooled-random for enzalutamide/apalutamide-treated patients: 0.690, 95% CI 0.568–0.838; p value < 0.001; $I^2 = 0.00\%$, $p = 0.72$; Fig. 2b.1).

Among patients treated with apalutamide or enzalutamide, the survival benefit was confirmed in previously untreated patients (pooled random HR 0.587, 95% CI, 0.467–0.736, $p < 0.001$, $I^2 = 0.00\%$, $p = 0.46$; Fig. 2b.2) but no survival benefit emerged in patients exposed (concomitant or subsequently) with docetaxel (pooled random HR 0.948, 95% CI 0.671–1.338, $p = 0.760$, $I^2 = 0\%$, $p = 0.48$; Fig. 2b.3).

Regarding rPFS analyses, we considered five of eight studies selected [5, 6, 10, 12–14] (three studies did not report data on rPFS [7–9, 11]). Overall, the administration of experimental compounds resulted in prolonged

rPFS in overall cohort (pooled random HR: 0.475, 95% CI 0.390–0.579, $p < 0.001$). Heterogeneity was statistically significant with an I^2 value of 74%, $p = 0.004$ (Fig. 3a). The radiological progression-free advantage was also achievable including patients previously untreated (Fig. 3b.1) and exposed (concomitant or subsequently) with docetaxel to docetaxel (in this case Heterogeneity was statistically significant. I^2 value: 81.62%, $p = 0.0002$; Fig. 3b.2).

When we consider only the three studies with a cohort of previously treated patients, the rPFS advantage was available in all patients, previously untreated patients (Fig. 3c.2) and previously treated patients (or patients who received concomitant docetaxel) (Fig. 3c.3). An extensive summary of the results achieved for this aim are available in the Supplementary Material.

In bPFS analyses, we collected data provided by four of eight studies [5, 6, 10, 13, 14]. In this analyses, administration of experimental compounds (docetaxel, enzalutamide or abiraterone) resulted in a significant improvement of bPFS, although heterogeneity was statistically significant ($I^2 = 93.99\%$, $p < 0.0001$). Similar results have been observed when analysis was restricted to patients who received

Table 1 Description of studies included in meta-analysis

GETUG-AFU-15 [5, 6]

Randomized, open-label, Phase 3 trial evaluating androgen-deprivation therapy (ADT) ± docetaxel (75 mg/m^2) in patients with radiologically proven mHSPC

Primary endpoint: overall survival (OS)

Secondary endpoints: clinical progression-free survival (cPFS), biochemical progression-free survival (bPFS)

No. of patients
192 in ADT + Docetaxel arm, 193 in ADT alone arm

Median follow-up
83.9 months

Primary endpoint (mOS)
Hazard ratio (HR): 0.88 (95% CI, 0.68–1.14, $p = 0.3$)

Secondary endpoints (bPFS, rPFS)
0.69 (95% CI, 0.55–0.87; $p = 0.002$);
HR: 0.67 (95% CI, 0.54–0.84; $p < 0.001$)

CHAARTED [7, 8]

Randomized, open-label, Phase 3 trial evaluating androgen-deprivation therapy (ADT) ± docetaxel (75 mg/m^2) in patients with radiologically proven mHSPC

Primary endpoint: overall survival (OS)

Secondary endpoints: time to development of castration resistant prostate cancer (TCRPC). Two amendments were made in this study: the first allowed the inclusion of patients with low volume metastatic disease (high volume metastatic disease was defined as: presence of visceral metastases or 4 or more bone lesions with one or more lesions beyond vertebral bodies and pelvis) and the second which expanded the initial overall cohort to 780 patients

No. of patients
397 in ADT + docetaxel arm, 393 in ADT alone arm

Median follow-up
53.7 months

Primary endpoint (mOS)
HR: 0.72 (95% CI, 0.59–0.89; $p = 0.0018$)

Secondary endpoints (TCRPC)
HR: 0.61 (95% CI, 0.52–0.73; $p < 0.001$)

STAMPEDE [9]

STAMPEDE is a multi-arm, multistage trial evaluating multiple distinct strategies in parallel against a single control arm. In this stage, patients with high risk, locally advanced, metastatic or recurrent hormono sensitive prostate cancer were randomized to receive ADT, ADT + zoledronic acid (ZA, 4 mg every 28 days), ADT + ZA + docetaxel (75 mg/mq) or ADT + docetaxel. Primary outcome was OS, secondary outcome failure free survival (FFS)

No. of patients
1184 ADT arm, 593 ADT + ZA, 593 ADT + ZA + docetaxel, 592 ADT + docetaxel

Median follow-up
43 months

Primary endpoint (mOS)
ADT vs ADT + ZA (HR = 0.94, 95% CI 0.79–1.11; $p = 0.45$)
ADT vs ADT + docetaxel (HR = 0.78, 95% CI 0.66–0.93; $p = 0.006$)
ADT vs ZA + docetaxel (HR = 0.82, 95% CI 0.69–0.97; $p = 0.022$)

Secondary endpoints (FFS)
ADT vs ADT + ZA (HR = 0.92, 95% CI 0.81–1.04, $p = 0.198$)
ADT vs ADT + docetaxel (HR = 0.61, 95% CI 0.53–0.70, $p < 0.001$)
ADT vs ZA + docetaxel (HR = 0.62, 95% CI 0.54–0.70; $p < 0.001$)

LATITUDE [10]

Double-blind, placebo-controlled, Phase 3 trial comparing ADT alone to ADT + abiraterone (1000 mg daily) + prednisone (5 mg daily). All patients enrolled in this study had a diagnosis of mHSPC. Moreover only patients with two of these risk factors have been enrolled: (1) Gleason of 8 or more, (2) visceral metastases, (3) three or more bone metastases

Primary endpoints: OS, rPFS

Secondary endpoints: time to the next "skeletal-related event", bPFS, time to next treatment, time to initiation of chemotherapy and time to pain progression

Table 1 (continued)

No. of patients
602 ADT + placebo + placebo arm, 597 ADT + abiraterone + prednisone arm

Median follow-up
30.4 months

Primary endpoints (*1. mOS, 2. rPFS*)
1. ADT + placebo + placebo vs ADT + abiraterone + prednisone (HR = 0.62, 95% CI, 0.51–0.76, *p* < 0.001)
2. ADT + placebo + placebo vs ADT + abiraterone + prednisone (HR = 0.47, 95% CI, 0.39–0.55, *p* < 0.001)

Secondary endpoints (*1. time to the next "skeletal-related event", 2. bPFS, 3. time to next treatment, 4. time to initiation of chemotherapy and 5. time to pain progression*)
1. ADT + placebo + placebo vs ADT + abiraterone + prednisone (HR = 0. 70, 95% CI 0.54–0.92, *p* = 0.009)
2. ADT + placebo + placebo vs ADT + abiraterone + prednisone (HR = 0.30, 95% CI 0.26–0.35, *p* < 0.001)
3. ADT + placebo + placebo vs ADT + abiraterone + prednisone (HR = 0.42, 95% CI 0.35–0.5, *p* < 0.001)
4. ADT + placebo + placebo vs ADT + abiraterone + prednisone (HR = 0.44, 95% CI 0.35–0.56, *p* < 0.001)
5. ADT + placebo + placebo vs ADT + abiraterone + prednisone (HR = 0.70, 95% CI 0.58–0.83, *p* < 0.001).

STAMPEDE [11]

STAMPEDE is a multi-arm, multistage trial evaluating multiple distinct strategies in parallel against a single control arm. In this stage, patients with newly diagnosed and metastatic, node-positive, or high-risk locally advanced (defined with the presence of two of these risk factors: T3–4, Gleason 8–10, PSA of 40 ng/mL or more) or patients with high-risk disease relapsing after radiation therapy or surgery (defined as a PSA > 4 ng/mL, with a doubling time < 6 months, PSA level > 20 ng/mL, nodal or metastatic relapse or < 12 months of total ADT with an interval of > 12 months without treatment) were randomized to receive ADT alone or ADT + abiraterone (1000 mg) + prednisone (5 mg). Of note, this was not a placebo-controlled trial. Primary outcome was OS while FFS was the intermediate primary endpoint. Adverse events, symptomatic skeletal events, PFS, prostate cancer specific survival and quality of life were secondary endpoints

No. of patients
957 ADT arm, 960 ADT + abiraterone + prednisone arm

Median follow-up
40 months

Primary endpoints (*1. mOS, 2. FFS*)
1. ADT vs ADT + abiraterone + prednisone (HR = 0.63, 95% CI 0.52–0.76, *p* < 0.001)
2. ADT vs ADT + abiraterone + prednisone (HR = 0.29, 95% CI 0.25–0.34, *p* < 0.001)

Secondary endpoints (*1. adverse events, 2. symptomatic skeletal events, 3. PFS, prostate cancer specific survival and 4. quality of life*)
1. ADT vs ADT + Abiraterone + prednisone (Grade 3–5 AEs occurred in 33% and 47% respectively)
2. ADT vs ADT + abiraterone + prednisone (HR = 0.46, 95% CI 0.37–0.58, *p* < 0.001)
3. ADT vs ADT + abiraterone + prednisone (HR = 0.40, 95% CI 0.34–0.47, *p* < 0.001)
4. Not reported

ARCHES [14]

Phase III randomized, placebo-controlled clinical trial comparing ADT + placebo vs ADT + enzalutamide (160 mg) in patients with mHSPC. Primary endpoint was rPFS and OS. Secondary endpoints are: bPFS, time to new anticancer treatment, PSA undetectable rate, objective response rate (ORR), time to deterioration in urinary symptoms. To date only data of rPFS final analysis and interim OS analysis have been published

No. of patients
576 ADT + placebo arm, 574 ADT + enzalutamide arm

Median follow-up
Not reported

Primary endpoints (*1. mOS, 2. rPFS*)
1. Only result of interim analysis reported (immature follow up)
2. ADT + placebo vs ADT + enzalutamide (HR = 0.39, 95% CI 0.30–0.50, *p* < 0.0001)

Secondary endpoints (1. bPFS, 2. time to new anticancer treatment, 3. PSA undetectable rate, 4. objective response rate, 5. time to deterioration in urinary symptoms):
1. ADT + placebo vs ADT + enzalutamide (HR 0.19, 95% CI 0.13–0.26, *p* < 0.0001)
2. ADT + placebo vs ADT + Enzalutamide (HR 0.28, 95% CI 0.20–0.40, *p* < 0.0001)
3. ADT + placebo vs ADT + enzalutamide (17.6% vs 68.1%, *p* < 0.0001)
4. ADT + placebo vs ADT + enzalutamide (63.7% vs 83.1%, *p* < 0.0001)
5. Not reported

Table 1 (continued)

ENZAMET [13]

Open-label, randomized, Phase 3 trial investigating the combination between enzalutamide (160 mg) and ADT versus ADT alone in patients with mHSPC. Primary endpoint was OS while bPFS, clinical PFS, radiological PFS and safety were secondary outcomes. After the enrollment of 88 patients, the early administration of docetaxel with testosterone suppression was permitted. Up to two cycles of docetaxel were permitted before randomization. Randomization was performed considering also the presence of high or low volume disease (high volume disease defined as defined as the presence of visceral metastases or at least four bone lesions with at least one lesion located beyond the vertebral bodies and pelvis)

No. of patients:
562 ADT, 563 ADT + enzalutamide arm

Median follow-up:
34 months

Primary endpoints (*1. mOS, 2. PFS*):
1. ADT vs ADT + enzalutamide arm (HR 0.67, 95% CI 0.52–0.86, $p = 0.002$)
2. ADT vs ADT + enzalutamide arm (HR clinical PFS = 0.40, 95% CI 0.33–0.49 $p < 0.0001$)

Secondary endpoints (*1. bPFS, 2. clinical PFS, and 3. safety*)
1. ADT vs ADT + enzalutamide arm (HR clinical PFS = 0.39, 95% CI 0.33–0.47 $p < 0.0001$)
2. ADT vs ADT + enzalutamide arm (HR clinical PFS = 0.40, 95% CI 0.33–0.49 $p < 0.0001$)
3 ADT vs ADT + enzalutamide arm (34% vs 42%)

TITAN [12]

Double-blind, Phase 3 trial comparing apalutamide (240 mg) to placebo in addition to standard ADT in patients with mHSPC. Previous docetaxel treatment was allowed. Primary endpoints were OS and rPFS. Secondary endpoint were: time to cytotoxic chemotherapy, time to pain progression, time to chronic opioid use, time to skeletal-related event

Randomization was performed considering also the presence of high or low volume disease (high volume disease defined as defined as the presence of visceral metastases or at least four bone lesions with at least one lesion located beyond the vertebral bodies and pelvis)

No. of patients
527 ADT + placebo, 525 ADT + apalutamide

Median follow-up
22.7 months

Primary endpoints (*1. mOS, 2. rPFS*)
1. ADT + placebo vs ADT + apalutamide (HR 0.67; 95% CI 0.51–0.89, $p = 0.005$)
2. ADT + placebo vs ADT + apalutamide (HR 0.48, 95% CI 0.39–0.60, $p < 0.001$)

Secondary endpoints (*1. time to cytotoxic chemotherapy, 2. time to pain progression, 3. time to chronic opioid use, 4. time to skeletal-related event, 5. bPFS*)
1. ADT + placebo vs ADT + apalutamide (HR 0.39, 95% CI 0.27–0.56, $p < 0.0001$)
2. Not performed
3 Not performed
4. Not performed
5. ADT + placebo vs ADT + apalutamide (HR 0.26, 95% CI 0.21–0.32, $p < 0.0001$)

Table 2 Risk of bias among trials included: + low risk of bias, − high risk of bias, ? uncertain risk of bias

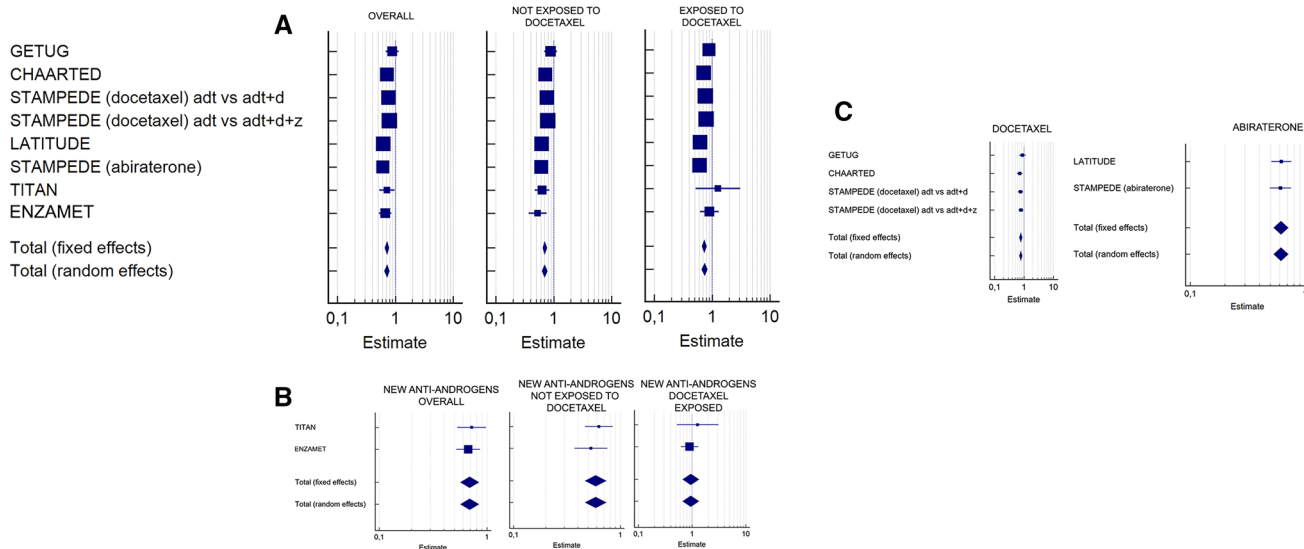| Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome and assessment	Incomplete outcome data	Selective reporting	Other bias
GETUG-AFU-15 [5, 6]	+	+	−	−	+	+	+
CHAARTED [7, 8]	+	+	−	−	+	?	+
STAMPEDE [9]	+	+	−	−	+	+	+
LATITUDE [10]	+	+	+	+	+	+	+
STAMPEDE [11]	+	+	−	−	+	+	+
ARCHES [14]	?	+	+	+	−	−	?
ENZAMET [13]	+	+	−	−	+	+	+
TITAN [12]	+	+	+	+	+	+	+

Fig. 2 Overall survival (OS) analysis among patients with metastatic hormone sensitive prostate cancer. **a** All patients included, including patients not previously exposed to docetaxel, patients previously exposed to docetaxel. **b** New anti-androgens overall, exposed and not previously exposed to docetaxel. **c** OS result among metastatic patients receiving docetaxel; OS result among metastatic patients receiving abiraterone
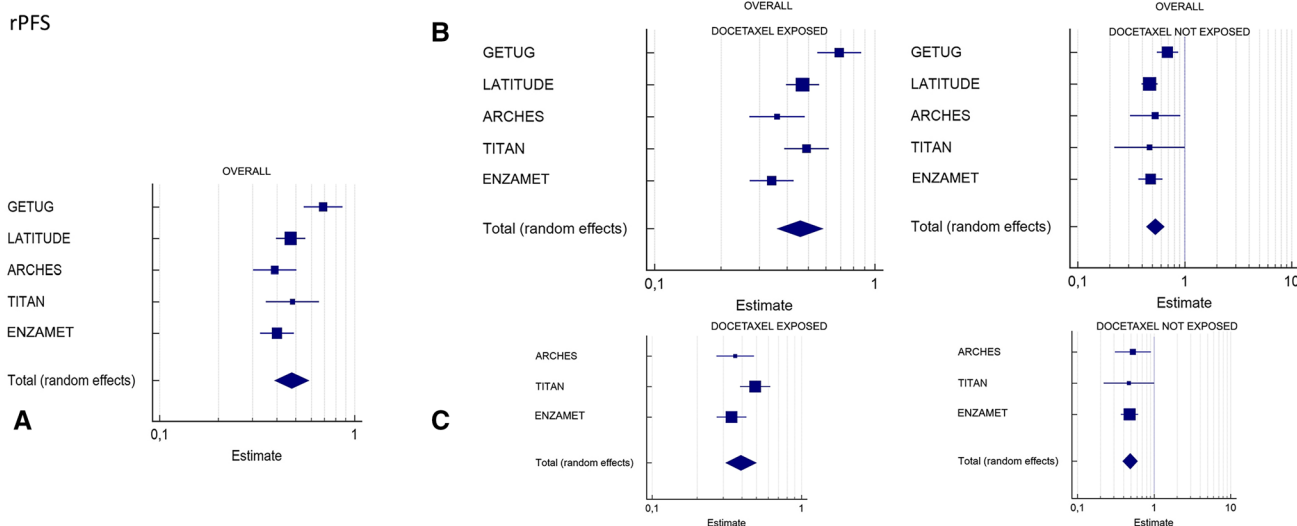

Fig. 3 Radiological progression-free (rPFS) analysis. **a** All studies reporting rPFS. **b** All studies including patients who received docetaxel before experimental treatment, all studies including patients not exposed to docetaxel. **c** New anti-androgen treatment among patients who did not receive docetaxel and among patients previously exposed to docetaxel

hormonal experimental compounds ($I^2 = 85.9\%$, $p = 0.0008$) or enzalutamide ($I^2 = 92.38\%$, $p = 0.0003$) (Table 3).

3.3 Subgroup Analysis

Variable of interest in subgroups analyses were: Eastern Cooperative Oncology Group (ECOG) performance status

0 versus ECOG performance status 1–2, aged < 70 years versus aged ≥ 70 years, Gleason < 8 versus ≥ 8, presence or absence of visceral metastases, high volume versus low volume disease, normal level versus high LDH (Table 3).

In ECOG performance status analysis, all agents showed an improvement in survival regardless of initial performance status (Table 3). Similarly, patients aged < 70 years

Table 3 Biochemical progression-free survival (bPFS) analysis and sub-group analysis [estimate (95% CI)] among studies included in meta-analysis

Study		ECOG 0	ECOG 1–2	Age < 70 y	Age ≥ 70 y	bPFS	Gleason < 8	Gleason ≥ 8	Visceral metastases no	Visceral metastases yes	High volume no	High volume yes	LDH normal	LDH high
GETUG [5, 6]		1.020 (0.749–1.389)	0.780 (0.151–4.023)			0.670 (0.537–0.836)	0.710 (0.437–1.153)	1.270 (0.869–1.857)			1.020 (0.671–1.551)	0.780 (0.559–1.088)	0.940 (0.640–1.380)	1.250 (0.616–2.535)
CHAARTED [7, 8]		0.710 (0.500–1.009)	0.420 (0.262–0.674)	0.430 (0.233–0.792)	0.430 (0.233–0.792)		0.410 (0.210–0.800)	0.600 (0.432–0.834)	0.640 (0.460–0.890)	0.520 (0.251–1.076)	1.040 (0.699–1.548)	0.630 (0.501–0.792)		
STAMPEDE (ADT+D vs ADT) [9]		0.770 (0.619–0.958)	0.790 (0.571–1.092)	0.730 (0.591–0.9029)	0.900 (0.641–1.2639)		0.670 (0.415–1.082)	0.760 (0.617–0.936)						
STAMPEDE (ADT+D+Z vs ADT) [9]		0.870 (0.709–1.068)	0.660 (0.479–0.909)	0.750 (0.607–0.926)	0.990 (0.715–1.371)		0.770 (0.495–1.198)	0.790 (0.638–0.978)						
LATITUDE [10]		0.640 (0.478–0.857)	0.610 (0.465–0.799)			0.300 (0.259–0.348)	0.620 (0.181–2.123)	0.630 (0.513–0.774)	0.660 (0.527–0.826)	0.510 (0.330–0.789)			0.510 (0.378–0.687)	0.740 (0.565–0.969)
STAMPEDE (abiraterone) [11]		0.690 (0.554–0.860)	0.500 (0.349–0.717)	0.510 (0.400–0.650)	0.940 (0.687–1.285)		0.760 (0.475–1.217)	0.590 (0.478–0.728)						
TITAN [12]		0.710 (0.475–1.061)	0.590 (0.396–0.880)				0.560 (0.327–0.960)	0.730 (0.524–1.017)	0.470 (0.297–0.743)	0.990 (0.552–1.776)			0.690 (0.475–1.003)	0.680 (0.371–1.245)
ENZAMET [13]		0.660 (0.472–0.923)	0.660 (0.447–0.974)	0.560 (0.389–0.807)	0.560 (0.389–0.807)	0.390 (0.327–0.465)	0.590 (0.300–1.160)	0.700 (0.505–0.970)	0.620 (0.469–0.819)	1.050 (0.543–2.031)	0.430 (0.258–0.716)	0.800 (0.594–1.077)		
ARCHES [14]						0.190 (0.134–0.269)								
Docetaxel	F	0.836 (0.737–0.948)	0.653 (0.533–0.801)	0.718 (0.621–0.830)	0.855 (0.686–1.064) NSS		0.664 (0.517–0.853)	0.788 (0.694–0.895)*			1.030 (0.772–1.375) NSS	0.675 (0.559–0.815)		
	R	0.836 (0.735–0.951)	0.637 (0.481–0.843)	0.705 (0.584–0.852)	0.786 (0.530–1.167) NSS		0.664 (0.517–0.853)	0.805 (0.639–1.015)* NSS			1.030 (0.772–1.375) NSS	0.676 (0.555–0.824)		
ORMONO	F	0.674 (0.583–0.780)	0.589 (0.496–0.698)	0.525 (0.429–0.642)	0.755 (0.595–0.958)*	0.317 (0.284–0.353)*	0.647 (0.477–0.877)	0.638 (0.564–0.723)	0.623 (0.538–0.721)	0.719 (0.528–0.980)				
	R	0.674 (0.583–0.780)	0.589 (0.496–0.698)	0.525 (0.429–0.642)	0.732 (0.441–1.216)* NSS	0.291 (0.212–0.400)*	0.647 (0.477–0.877)	0.638 (0.564–0.723)	0.623 (0.538–0.721)	0.774 (0.471–1.270) NSS				

Table 3 (continued)

Study		ECOG 0	ECOG 1–2	Age <70 y	Age ≥70 y	bPFS	Gleason <8	Gleason ≥8	Visceral metastases no	Visceral metastases yes	High volume no	High volume yes	LDH normal	LDH high
Abiraterone	F	0.671 (0.563–0.800)	0.568 (0.457–0.705)				0.741 (0.477–1.149) NSS	0.610 (0.527–0.707)						
	R	0.671 (0.563–0.800)	0.568 (0.457–0.705)				0.741 (0.477–1.149) NSS	0.610 (0.527–0.707)						
Apalutamide Enzalutamide	F	0.680 (0.526–0.880)	0.625 (0.473–0.826)			0.336 (0.287–0.394)*	0.571 (0.375–0.871) NSS	0.715 (0.566–0.902)	0.575 (0.454–0.730)	1.016 (0.656–1.573) NSS				
	R	0.680 (0.526–0.880)	0.625 (0.473–0.826)			0.277 (0.137–0.559)*	0.571 (0.375–0.871) NSS	0.715 (0.566–0.902)	0.574 (0.451–0.732)	1.016 (0.656–1.573) NSS				
Overall	F	0.762 (0.693–0.838)	0.615 (0.539–0.701)	0.645 (0.574–0.726)	0.807 (0.687–0.948)*	0.366 (0.332–0.403)*	0.657 (0.542–0.797)	0.707 (0.647–0.773)*	0.623 (0.538–0.721)	0.684 (0.515–0.910)	0.833 (0.648–1.071)* NSS	0.708 (0.604–0.831) NSS	0.655 (0.537–0.800)	0.773 (0.613–0.976)
	R	0.761 (0.685–0.844)	0.615 (0.539–0.701)	0.621 (0.512–0.752)	0.768 (0.585–1.009)* NSS	0.354 (0.233–0.538)*	0.657 (0.542–0.797)	0.720 (0.627–0.826)*	0.623 (0.538–0.721)	0.709 (0.477–1.054)	0.786 (0.465–1.330)* NSS	0.708 (0.604–0.831) NSS	0.680 (0.477–0.971)	0.775 (0.610–0.986)

NSS not statistically significant, *F* fixed effect, *R* random effect

*Statistically significant heterogeneity

showed clear survival advantages with experimental treatments without particular differences among the classes of compounds adopted. However, patients aged ≥ 70 years did not show a clear survival benefit with experimental compounds and especially with the administration of docetaxel (a survival advantage emerged adopting fixed-effect model; however, due to the high level of heterogeneity observed, the pooled HR obtained with random-effect model should be considered).

Among patients with Gleason < 8, docetaxel and new anti-androgen compounds were associated with improved survival. Abiraterone did not prolong the OS of patients with low Gleason score (Table 3). In patients with higher Gleason score, the survival benefit was unclear with administration of docetaxel while both abiraterone and new anti-androgen were clearly associated with improved survival.

Data on efficacy in patients with visceral metastases were available in four of eight studies [7, 8, 10, 12, 13]. Of note, administration of apalutamide or enzalutamide did not reflect a statistically significant survival advantage in patients with visceral metastases (Table 3). Similarly, administration of docetaxel did not lead to an OS benefit in patients with low volume metastatic disease.

Patients with high serum level of LDH benefit from administration of abiraterone, while neither docetaxel nor apalutamide showed improved survival in this population. A detailed description of the results achieved in sub-group analyses is available in the Supplementary Material.

3.4 Safety Analysis

Overall, 9876 patients were included in safety analyses. Of these, 4865 received ADT while 5011 received experimental compounds (1807 docetaxel, 1545 abiraterone + prednisone, 1135 enzalutamide, 524 apalutamide).

In this analysis, administration of docetaxel was significantly associated with an increased RR to develop G3 or more neutropenia and neutropenia febrile (Table 4). There was no significant increased risk of high-grade anemia and thrombocytopenia observed with administration of docetaxel. Hormonal treatments were shown to prevent the onset of high-grade anemia. Docetaxel was associated with an increased risk of sensory toxicity.

In fatigue analyses, all agents were associated with increased risk of fatigue development. However, heterogeneity of studies evaluating docetaxel was statistically significant and no increased risk of high-grade fatigue emerged with abiraterone. Only administration of new hormonal anti-androgen was clearly associated with increased risk of this AE.

RR of seizure/dizziness, falls, arthralgia and edema resulting from enzalutamide/apalutamide administration were not statistically significant.

Increased risk of high-grade cardiovascular toxicity was clearly associated with abiraterone + prednisone treatment, while the risk of hypertension was not statistically relevant in patients receiving apalutamide or enzalutamide.

Risk of death due to AE was unclear in patients treated with docetaxel, while patients who received abiraterone or new-antiandrogen compounds did not show an increased risk of death (Table 4). An extensive description of the result obtained in safety analysis is available in the Supplementary Material.

4 Discussion

Here we report the result of a meta-analysis exploring the role of chemotherapy and new hormonal treatments in addition to ADT in patients with mHSPC.

Our results showed that all these agents are able to improve OS with the exception of the anti-androgen (apalutamide and enzalutamide) in patients previously exposed to docetaxel. Considering that all these agents showed a survival benefit in randomized clinical trials, our findings are not surprising. However, important data may be suggested by subgroup analyses.

Overall, all agents were also able to improve rPFS and bPFS, while the results of this last analysis were weighted by a large heterogeneity. Of interest, we isolated a specific subgroup of patients who may present worst survival after docetaxel (patients aged ≥ 70 years, high Gleason score at diagnosis, and higher LDH serum levels), abiraterone + prednisone (low Gleason score) and apalutamide/enzalutamide (visceral metastases, previously or concomitant docetaxel-exposed patients, high LDH serum levels) treatment.

There are several limitations, which may reduce the value of our analyses. First of all the included studies presented a heterogeneous population, which often consists of patients with both metastatic and non-metastatic disease (only patients with metastatic disease were included in OS and rPFS analyses) [9, 11], patients with different volume and risk [5–11] and patients previously exposed to other systemic treatment in addition to ADT [12–14]. Another limitation is the inclusion of data of sub-groups and exploratory analyses, which have the limitation of being previously unplanned analysis among trials explored. In subgroup analysis, some studies reported survival outcomes in patients aged < 65 years or > 65 years and thus, the same studies have not been included in this subgroup analysis. Moreover, age alone is not a useful variable as it does not take in account patients' clinical conditions, comorbidities and performance status. Thus, age alone should be not be used as a parameter for planning therapeutic choices in clinical practice. Similarly, some studies [12, 14] randomized patients in ECOG performance status 0 or 1 (without enrollment of ECOG, 2

Table 4 High grade AE analysis among studies included [relative risk (95% CI)]

Study		Anemia	Thrombocytopenia	Neutropenia	Febrile neutropenia	Sensory toxicity	Fatigue	Arthralgia	Cardiological toxicity	Hypertension	Edema	Falls	Seizure	Death
GETUG [5, 6]		1.968 (0.365–10.617)	3.000 (0.123–73.182)	121.058 (7.542–1943.099)	30.511 (1.839–506.253)	6.889 (0.358–132.469)	6.397 (1.464–27.958)							8.858 (0.480–163.387)
CHAARTED [7, 8]		11.056 (0.613–199.282)	7.000 (0.363–135.076)	95.486 (5.907–1543.594)	49.251 (3.005–807.078)	9.046 (0.489–167.464)	33.169 (1.997–550.963)							5.026 (0.242–104.348)
STAMPEDE (ADT+D vs ADT) (ADT+D+Z vs ADT) [9]				18.519 (8.201–41.820)	9.144 (5.419–15.429)	1.649 (0.966–2.817)	1.698 (1.202–2.400)		0.868 (0.547–1.377)					1.736 (0.595–5.064)
LATITUDE [10]		0.560 (0.301–1.042)					0.720 (0.322–1.609)		3.361 (1.359–8.311)	2.034 (1.525–2.712)				1.176 (0.690–2.005)
STAMPEDE (Abiraterone) [11]		0.591 (0.234–1.494)	5.000 (0.240–104.014)	5.063 (1.112–23.048)	2.025 (0.372–11.032)		1.418 (0.735–2.733)	2.430 (0.860–6.872)	2.209 (1.088–4.485)	3.427 (1.858–6.322)	11.139 (0.617–201.177)			3.038 (0.825–11.187)
TITAN [12]		0.532 (0.240–1.184)					1.341 (0.469–3.838)	0.402 (0.0784–2.064)		0.922 (0.624–1.363)		1.006 (0.253–4.000)	3.017 (0.123–73.899)	0.629 (0.288–1.372)
Enzamet [13]		0.793 (0.214–2.937)		1.920 (1.062–3.471)	1.146 (0.725–1.812)	4.955 (0.580–42.2834)	1.920 (1.062–3.471)		1.133 (0.558–2.299)	1.705 (1.056–2.752)		2.973 (0.603–14.669)	4.956 (0.238–102.997)	0.850 (0.287–2.512)
ARCHES [14]							11.038 (0.612–199.174)	0.502 (0.0923–2.729)		1.907 (0.894–4.064)	1.003 (0.0629–16.005)			
Docetaxel	F	3.771 (0.944–15.058) NSS	4.984 (0.585–42.432)	30.646 (14.608–64.293)	10.947 (6.628–18.081)	1.932 (1.162–3.212)	2.185 (1.580–3.020)*							2.559 (1.019–6.425)
	R	3.173 (0.658–15.289) NSS	4.711 (0.537–41.305)	35.530 (9.108–138.600)	10.529 (5.634–19.676)	1.965 (0.971–3.977) NSS	4.678 (0.972–22.521)* NSS							2.296 (0.885–5.960) NSS
ORMONO	F	0.578 (0.383–0.871)		2.266 (1.314–3.909)	1.197 (0.770–1.862) NSS		1.470 (1.036–2.086)		1.943 (1.265–2.983)					1.123 (0.796–1.583) NSS
	R	0.578 (0.383–0.872)		2.409 (1.072–5.413)	1.191 (0.765–1.855) NSS		1.402 (0.886–2.219) NSS		1.948 (1.060–3.578)					1.115 (0.743–1.673) NSS

Table 4 (continued)

Study		Anemia	Thrombocytopenia	Neutropenia	Febrile neutropenia	Sensory toxicity	Fatigue	Arthralgia	Cardiological toxicity	Hypertension	Edema	Falls	Seizure	Death
Abiraterone	F	0.570 (0.340–0.954)					1.081 (0.654–1.784) NSS		2.617 (1.501–4.560)	2.281 (1.758–2.960)				1.383 (0.850–2.251) NSS
	R	0.569 (0.340–0.954)					1.053 (0.545–2.035) NSS		2.591 (1.483–4.525)	2.457 (1.499–4.027)				1.559 (0.665–3.654) NSS
Apalutamide Enzalutamide	F	0.592 (0.300–1.168)					1.968 (1.194–3.244)	0.447 (0.138–1.446) NSS		1.277 (0.968–1.686) NSS				0.911 (0.558–1.486) NSS
	R	0.593 (0.300–1.173)					1.864 (1.122–3.097)	0.448 (0.138–1.451) NSS		1.363 (0.842–2.207) NSS				0.912 (0.554–1.500) NSS
Overall	F	0.705 (0.482–1.029) NSS	5.000 (0.868–28.807)	10.536 (6.996–15.868)*	4.447 (3.282–6.024)	1.932 (1.162–3.212)	1.829 (1.443–2.317)	1.153 (0.564–2.356) NSS	1.354 (0.995–1.843) NSS	1.746 (1.447–2.107)*	4.372 (0.743–25.725) NSS	1.665 (0.606–4.570) NSS	3.990 (0.446–35.677) NSS	1.261 (0.916–1.734) NSS
	R	0.684 (0.430–1.087) NSS	4.822 (0.825–28.189)	13.904 (2.423–79.801)*	5.869 (1.301–26.486)	1.965 (0.971–3.977) NSS	1.763 (1.131–2.746)*	0.915 (0.264–3.171) NSS	1.533 (0.840–2.798) NSS	1.781 (1.173–2.704)*	3.227 (0.281–37.034) NSS	1.602 (0.558–4.598) NSS	3.918 (0.434–35.401) NSS	1.241 (0.847–1.819) NSS

NSS not statistically significant, *F* fixed effect, *R* random effect

*Statistically significant heterogeneity

patients) and this may further underestimate the value of ECOG performance status subgroup analysis. Of note, we included two docetaxel arms of STAMPEDE trial in our analysis and this could translate in an over estimation of the overall effect. However, due to the missing impact of zoledronic acid on survival, it may be reasonable think that it did not influence the effect of docetaxel on OS.

Finally, our analysis stands alone as a quality of life comparison among experimental treatments and a cost-effectiveness evaluations.

Another important limitation emerged in the comparison of new anti-androgens after or during docetaxel treatment. Indeed, the settings in which docetaxel was administered was significantly different (previous docetaxel in TITAN study, concomitant docetaxel in ENZAMET trial) [12, 13]. This limited the value of our finding. However, in both subgroup analyses, patients who were previously exposed or patients with concomitant docetaxel did not seem to show a survival benefit from the addition of new anti-androgens. The limited number of patients considered, the high heterogeneity and the different modality of docetaxel administration (previous or concomitant) significantly limited the value of this analysis. Moreover, in the apalutamide arm, only 11 events occurred, and median overall survival is still not mature. Significantly higher percentage of patients who received docetaxel have been included in enzalutamide arm.

These limitations are mainly due to the lack of data on quality of life in patients receiving new anti-androgen.

Despite these issues, our meta-analysis is, to the best of our knowledge, the largest meta-analysis carried out on patients with mHSPC and offers a valuable insight into the management of the disease.

Overall survival benefit emerged with all agents considered (docetaxel, abiraterone and enzalutamide) and this is consistent with the single result reported by the trials considered. STAMPEDE, GETUG and ARCHES trials failed to report a significant improvement in terms of OS. This may be explained by an Inadequate selection of patients randomized to receive docetaxel (STAMPEDE and GETUG) or in a still immature OS follow up (ARCHES) [5, 6, 9, 14]. However, pooled-HR of studies adopting the same agents confirmed that each agent was associated with survival improvement raising the key value of a good selection of patients before treatment planning.

Of note, we identified that patients with high baseline LDH serum levels did not show a survival benefit with the addition of new anti-androgens. This result should be carefully evaluated as only three studies reported sub-group analysis in this subpopulation of patients [5, 6, 10, 12] and this might have influenced the final results. Indeed, only TITAN study [12] reported complete data about patients with low/high LDH, while no information is available from ARCHES and ENZAMET studies [13, 14]. Overall, enzalutamide was

shown to be an effective treatment in patients with high volume disease [13] while neither enzalutamide nor apalutamide have shown any real advantage in patients with visceral metastases [12, 13].

Curiously, we detected a low level of heterogeneity in OS analysis, while higher heterogeneity emerged in rPFS and bPFS analyses. It is likely that the different modalities and timing of assessment influenced these results, increasing heterogeneity of rPFS and bPFS outcome. In particular, the high level of heterogeneity emerging from bPFS analysis may reflect the different definition and assessment that had been adopted by the clinical trials included. Thus, this analysis should be carefully interpreted as potentially affected by these biases. GETUG [5, 6] study provided significantly worse results in terms of rPFS and bPFS and was the only trial to adopt docetaxel in rPFS and bPFS. The results of this trial probably affected the high level of heterogeneity observed.

The selection of patients with mHSPC is a well-known issue, which emerged during primary studies evaluating docetaxel in this population. The evidence that patients with high-volume disease benefit from docetaxel, while in patients with low-volume disease, there was no clear evaluation of the results of GETUG-AFU-15, CHAARTED, and STAMPEDE trials [5–9]. Subsequently the combination ADT + abiraterone + prednisone was tested in patients with high-risk disease and in patients with lowest stage/grade of disease showing positive results on OS [10, 11]. A meta-analysis that aimed to compare OS in patients receiving docetaxel or abiraterone, failed to show a significant difference between these treatments [23, 24]. Subsequently, another analysis suggested that abiraterone + prednisone may be the most effective treatment; however, heterogeneity and variability of patients included in trials under investigation may have affected the final result [25].

Prevention of disease progression and better quality of life also emerged in a comparison analysis between docetaxel and abiraterone [26].

Toxicity may be another important issue to consider before treatment planning. In our study, we confirmed the classical hematological toxicity of docetaxel and also the sensorial neuropathy associated with this treatment. Abiraterone + prednisone were significantly associated with an increased risk of cardiological toxicity and hypertension, confirming the result of a previous analysis of this AE [26].

Classical AE of interest among new anti-androgen compounds are dizziness/seizures, falls and mental impairment. In our analysis, we showed that the risk of high-grade dizziness/seizures is low and infrequent during new anti-androgen treatment. Unfortunately, we were not able to perform an evaluation of mental impairment AE due to the lack of complete data and maybe the still immature follow-up. Curiously, an increased risk of neutropenia emerged with

the administration of hormonal agents (no increased risk of febrile neutropenia). This outcome may reflect other complications related to prostate cancer (such as cancer medullary replacement and consequent neutropenia) more than a specific toxicity of hormonal treatment.

Of note, risk of death during the course of treatment was similar among the experimental and comparator arms. The inclusion of grade 3 or more AEs may limit the real impact of some toxicity. Indeed, low-grade fatigue (such as grade 2) may be an important toxicity experienced by patients, significantly reducing their quality of life.

Our analysis confirms the well-known toxicity profiles of new anti-androgens, docetaxel and abiraterone and does not add significant insight in the safety profile of these agents. However, summarizing evidences about safety profile of agents available for management of mHSPC may be an important issue, as this is a key element to plan our choices in clinical practice.

5 Conclusion

The addition of chemotherapy, abiraterone or new anti-androgens to ADT improves survival of patients with mHSPC. Our finding is not surprising considering results achieved by each drug in randomized studies.

The use of a new anti-androgen may not improve survival of patients receiving concomitant docetaxel or previous docetaxel. However, the large heterogeneity among studies evaluating this issue limits the value of this observation. According to our results, patients with visceral metastases did not seem to show a survival benefit with the administration of new anti-androgens. Initial Gleason score may be related to different outcomes among patients receiving docetaxel or abiraterone. Toxicity profiles of these drugs confirmed the known hematological toxicity of docetaxel and cardio-vascular toxicity associated with abiraterone. High-grade AEs typically associated with new anti-androgens rarely occur during or after treatment.

Results of our meta-analysis suggest that:

- Patient selection is essential before treatment planning. Indeed, some patients do not benefit from a specific treatment (such as docetaxel for patients with low tumor volume or enzalutamide/apalutamide in patients previously exposed to chemotherapy)
- Disease assessment may be an important issue to consider before treatment planning. Low Gleason score may be associated with lowest effect of abiraterone on survival. The presence of visceral metastases should discourage the adoption of apalutamide or enzalutamide.
- Toxicity profile of agents should be carefully considered, and administration of enzalutamide/apalutamide may be

a treatment of choice in frail patients. The cardiotoxicity of abiraterone should be considered in patients with high number of cardiovascular comorbidities, while patients with hematopoietic dysfunction or higher risk of infective disease should be discouraged from the adoption of docetaxel in this setting.

Compliance with Ethical Standards

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