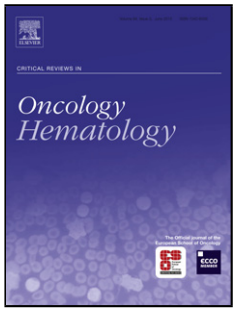

First-line systemic therapy for metastatic castration-sensitive prostate cancer: an updated systematic review with novel findings

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First-line systemic therapy for metastatic castration-sensitive prostate cancer: an updated systematic review with novel findings

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Analysis and interpretation of data: all authors

Drafting of the manuscript: Felice Crocetto, Carlo Buonerba

Critical revision of the manuscript for important intellectual content: all authors

Statistical analysis: Pasquale Dolce

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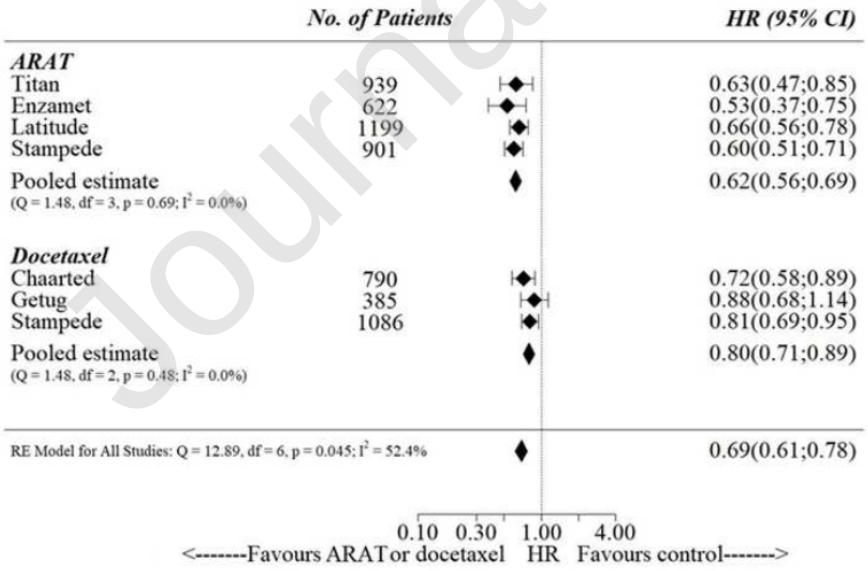
Graphical Abstract



Abstract

Although both docetaxel and androgen-receptor-axis-targeted (ARAT) agents have yielded survival improvements in combination with androgen deprivation therapy (ADT) compared to ADT alone in metastatic castration-sensitive prostate cancer (mCSPC) patients, the optimal therapeutic choice remains to be established. We analyzed estimates of the hazard ratios for death (OS-HRs) in patients treated in the first-line setting enrolled in the GETUG-AFU15, CHAARTED, STAMPEDE, LATITUDE, ENZAMET, and TITAN trials. Overall, men with castration sensitive prostate cancer receiving either an ARAT agent or docetaxel as first-line systemic therapy showed a pooled OS-HR of 0.69 (95% CI: 0.61-0.78), with significant heterogeneity (p=0.045, I^2 = 52.5%). Network meta-analysis showed an OS-HR in patients receiving an ARAT agent vs. docetaxel of 0.78 (95%CI: 0.67-0.91). In conclusion, the evidence analysed indicates that an ARAT agent may provide improved OS outcomes compared to docetaxel. Prospective randomized trials are warranted.

Keywords: castration-sensitive prostate cancer, abiraterone, enzalutamide, apalutamide

1. Introduction

Prostate cancer represents 7.1% of all malignancies diagnosed in men, with an estimated 358,989 deaths in 2018[1]. The majority of prostate cancer-related deaths occur in patients who develop metastatic disease that progresses despite hormonal therapy, that is metastatic castration-resistant prostate cancer (mCRPC) [2]. Over the past five years, large randomized-controlled trials (RCTs) have shown that several systemic therapies that are effective in the castration-resistant setting [3] can also improve outcomes compared to androgen deprivation therapy (ADT) alone in men with metastatic castration-sensitive prostate cancer (mCSCP)[4], who may present alterations in androgen-receptor

pathway genes in up to 50% of cases[5]. Although both chemotherapy agent docetaxel [6] and androgen-receptor-axis-targeted (ARAT) agents apalutamide [7][8], abiraterone [9][10] and enzalutamide [11] [12] have shown to be effective in the metastatic-castration sensitive setting, there is a lack of consensus regarding optimal treatment choice [13]. While some data seem to suggest that docetaxel may not be effective in mCSPC men with low volume disease [6], there is uncertainty about the optimal definition of high vs. low burden disease and its underlying biology [14]. Given the absence of direct comparisons among docetaxel and ARAT agents in mCSPC patients, a few meta-analyses have attempted to establish optimal treatment both in unselected patient populations [15][16] and in selected patient sub-groups [17]. One recently published meta-analysis by Sathianathen et al. concluded that combination therapy of ADT plus either apalutamide, enzalutamide, abiraterone acetate or docetaxel was associated with a significant OS benefit with respect to ADT alone, with no evidence that any of these combinations may be more effective than another in terms of OS advantage [15]. Consistent results were obtained in another meta-analysis conducted by Marchioni et al, who concluded that ADTplus an ARAT agent in men with mCSPC was not associated with a more longer OS benefit compared to ADT plus docetaxel [16].

Our work group has previously focused on potential predictors of ARAT agents efficacy in mCPSC men and found that enzalutamide, abiraterone and apalutamide were associated with a pooled OS-HR of 0.66 (95 % CI: 0.60−0.74) [18]. Of note, no significant heterogeneity was reported among the trials testing an ARAT agent plus ADT vs. ADT alone in terms of OS advantage ($p = 0.87$, $I^2 = 0.0$ %). On the grounds of this finding, we pooled together data obtained with the novel ARAT agents in order to explore potential differences in efficacy with respect to docetaxel in mCSPC men. Although this topic has been intensively researched, the analysis presented here has not been performed so far to the best of our knowledge.

2 . Methods

2.1 Network meta-analysis design and search criteria

The objective of this net-work meta-analysis was to establish the best systemic treatment choice between docetaxel and ARAT agents in unselected patients with mCSPC who have not received

another systemic treatment other than ADT. We performed a systematic review to retrieve abstracts/presentations and full papers that reported the (OS-HRs) obtained in two-arm RCTs conducted in mCSPC patients receiving an ARAT agent or docetaxel plusADT vs. ADT with or without standard not steroidal therapy.

The systematic review was conducted by querying PubMed, Cochrane Library and EMBASE for relevant articles following the PRISMA guidelines. The following keywords were used for the search: prostate cancer, hormone sensitive, castration sensitive, metastatic. Details of the search criteria employed are reported in Appendix 1. Articles published since inception until October, 30st 2020 were assessed for inclusion in the systematic review. Abstracts and presentations from ASCO (American Society of Clinical Oncology), ASCO GU, ESMO (European Society of Medical Oncology) as well as EMUC (European Multidisciplinary Congress on Urological Cancers) since 2010 until 2020 were also considered. Articles that were referred to in the full papers retrieved were also evaluated for inclusion in this meta-analysis. Abstracts that provided relevant original data were included if unavailable as full papers. If duplicate publications were found, the publication reporting the most updated data were considered. Included RCTs was assessed for quality using the Jadad scale [19]. We also used The Cochrane Collaboration's tool to assess the risk of bias of the trials included[20]

2.2 Statistical analysis

Pooled OS-HR with the corresponding 95% CI was obtained using random-effects models the restricted maximum-likelihood estimator for estimating the variance of the distribution of effects. Pooled estimates of OS-HRs were also reported separately for trials testing an ARAT agent and trials testing docetaxel. The heterogeneity among studies was evaluated using the χ^2 Q test and I^2 statistics. For the Q test, significant heterogeneity was declared if $p < 0.05$, while I^2 values >50% were considered to indicate heterogeneity. Heterogeneity was evaluated for all trials, and separately for ARAT agents and docetaxel trials. A network meta-analysis was performed to compare overall efficacy

of ARAT agents vs. docetaxel using a frequentist approach. We performed a random effects model and ranked competing treatments by P scores ranging from 0 to 1 and obtained from the p-values of all pairwise comparisons. A higher score implies a better treatment. Publication bias was evaluated by visually assessing asymmetry on funnel plots of OS-HRs centred at comparison-specific effect against standard errors. Test for funnel plot asymmetry was not possible because of the small number of studies. The R statistical software, version 4.0.2, was used for all statistical analyses. Meta-analysis was performed using metafor package, version 2.1–0. Network meta-analysis was conducted using the netmeta R package. A p-value <0.05 was adopted to denote statistical significance.

3. Results

3.1. Eligible articles and trials

Our database search retrieved 7338 abstracts that were initially reviewed. Of the 223 full-texts of clinical studies presenting original data obtained in mCSPC, 8 full text articles reporting data from RCTs of men randomized to docetaxel or an ARAT agent vs. ADT-based therapy were considered after removing duplicate publications. Seven[6][7] [9] [11] [21] [22] [23] articles were finally included in this quantitative meta-analysis, after excluding the ARCHES [12] trial that did not report HR-OS in the subgroup of men who were naïve to docetaxel. Furthermore, HR-OS data reported in the ARCHES trial for the entire cohort were also immature. The flow chart of the systematic review is reported in figure 1.

Six different RCTs (LATITUDE, STAMPEDE, TITAN, GETUG-AFU15, ENZAMET, CHAARTED) were included in this analysis. All included trials were randomized-controlled, two-arm phase III trials. The LATITUDE [9] trial was a placebo-controlled trial including mCSPC patients with at least 2 of 3 high-risk features, including presence of measurable visceral metastasis, a Gleason score of 8 or more, ≥3 bone metastases. The STAMPEDE [21] [22] trial was a large randomized, open-label study based on an innovative multi-arm multi-stage platform design, including patients with both metastatic and non-metastatic castration-sensitive prostate cancer who were randomized to multiple systemic therapies, including docetaxel and abiraterone, in addition to the standard of care. While the LATITUDE trial had

a Jadad score of 5, the STAMPEDE trial had a Jadad score of 3 because of the lack of double blindness. The ENZAMET [11] trial was an open-label (Jadad score, 3) trial testing enzalutamide in men with mCSPC plus ADT compared to standard nonsteroidal antiandrogen therapy, while the double-blinded TITAN [7] trial randomized mCSPC men to apalutamide plus ADT vs. placebo plus ADT, with docetaxel being allowed before enrollment in the trial (Jadad score, 5). Both the CHAARTED [6] and the GETUG-AFU 15 [23] trials were randomized-controlled trials comparing docetaxel plus ADT vs. ADT alone in mCSPC men, with a Jadad score of 3. Risk of bias according to the Cochrane Collaboration's tool is reported in table 2. The main sources of bias are represented by the open-label study design and Aspects of study design and salient characteristics of the population enrolled of the trials included are reported in table 1. The evaluation of the included trials confirmed that study design, patient characteristics and methodology were similar among the selected studies, making the available findings suitable for a network meta-analysis.

3.2 Quantitative synthesis

HR-OS data obtained in a total of 5922 mCSPC men enrolled in the six RCT trials included who had not received a systemic therapy other than ADT at the time of enrollment were analyzed in this meta-analysis. For trials including men who had received a systemic agent other than ADT, OS-HRs obtained in the subgroup of patients who had received no systemic therapy other than ADT were included in the quantitative analysis. Overall, men on ADT treated with vs. without either therapy between docetaxel or an ARAT agent showed a pooled hazard ratio for death of 0.69 (95% CI: 0.61-0.78), with significant heterogeneity ($p=0.045$, $I^2 = 52.5\%$). Men on ADT treated with vs. without an ARAT agent as first-line additional systemic therapy for mCSPC showed a pooled HR for death of 0.62 (95%CI: 0.56-0.69), with no significant heterogeneity ($p=0.69$, $I^2 = 0\%$). Finally, men on ADT treated with vs. without docetaxel as first-line additional systemic therapy for mCSPC showed a pooled HR for death of 0.80 (95%CI: 0.71-0.89), with no significant heterogeneity ($p=0.48$, $I^2 = 0.0\%$). Network meta-analysis showed a HR for death in patients receiving an ARAT agent vs. docetaxel of 0.78 (95%CI: 0.67-0.91), suggesting a greater OS benefit associated with the use of an ARAT agent. Treatment ranking analysis also showed that an ARAT-based therapy was the preferred treatment over docetaxel. Visual assessment of funnel plots did not show an evident publication bias (figure 3).

4. Discussion

Although both docetaxel and androgen-receptor-axis-targeted (ARAT) agents have yielded survival improvements in combination with androgen deprivation therapy (ADT) compared to ADT alone in metastatic castration-sensitive prostate cancer (mCSPC) patients enrolled in large, randomized-controlled phase III trials, the optimal therapeutic choice remains to be established in this setting. An international panel of 72 experts in prostate cancer gathered in 2019 was unable to reach a consensus regarding optimal treatment choice among docetaxel, apalutamide, enzalutamide and abiraterone in high- vs. low- volume disease as well as in de novo vs. recurrent after local treatment metastatic castration-sensitive disease [13]. A consensus was reached in favour of the use of some form of single agent treatment and against the combined use of docetaxel plus an ARAT [24]. This result is consistent with the findings of our previous meta-analysis reporting a lack of a survival advantage in mCSPC men who received ADT plus an ARAT agent vs. ADT alone if they were concurrently treated or had been pre-treated with docetaxel vs. those who were naïve to docetaxel (interaction OS-HR = 1.77; 95 % CI = 1.12–2.77; p = 0.0134) [18]. Notably, in a retrospective analysis of the STAMPEDE trial including 189 patients receiving docetaxel and 377 men receiving abiraterone acetate in addition to standard of care, no difference in overall survival was reported (HR = 1.16; 95% CI: 0.82-1.65). Conversely, a statistically significant advantage was found in patients receiving abiraterone vs. those receiving docetaxel in failure-free survival (HR = 0.51; 95% CI: 0.39-0.67) and progression-free survival (HR = 0.65;95% CI: 0.48-0.88) [25].

To the best of our knowledge, two meta-analyses have quantitatively assessed differences among docetaxel, enzalutamide, abiraterone and apalutamide. Sathianathen et al have assessed published randomized-controlled trials testing docetaxel, abiraterone acetate, enzalutamide, or apalutamide plus ADT and concluded that all these agents prolonged OS with respect to ADT alone, with no significant heterogeneity in OS among the different agents explored [15]. Similarly, Marchioni et al concluded that neither enzalutamide or abiraterone or apalutamide yielded improved outcomes in terms of overall

survival when compared to docetaxel [16]. These conclusions were drawn by comparing single ARAT agents vs. docetaxel following a net-work meta-analysis approach. In this work, we rather approached the question of optimal systemic treatment by comparing survival outcomes between docetaxel vs. ARAT agents analysed a single class. The rationale for our approach is obviously based on their common pharmacodynamic profile, as also shown by cross-resistance between abiraterone and enzalutamide [26], as well on their similar efficacy in the castration-sensitive setting. In fact, in our recently published meta-analysis, we found no heterogeneity in HR-OS among apalutamide, enzalutamide and abiraterone (I^2=0,0%, Q=1.26, p=0.87) [18].

In the meta-analysis presented here, we included the GETUG-AFU15, CHAARTED, STAMPEDE, ENZAMET, and TITAN trials and excluded the ARCHES trial from the OS analysis because of immature OS data and of the lack of OS data in docetaxel-naïve patients. For the purposes of this meta-analysis, we only considered the sub-group of patients of the TITAN and ENZAMET studies that had not been exposed to docetaxel. Surprisingly, we found that pooled OS-HR associated with ARAT agents vs. docetaxel was 0.62 vs. 0.8, with non-overlapping 95% CIs (0.56-0.69 vs. 0.71-0.89). Furthermore, our network meta-analysis approach showed that an ARAT agent vs. docetaxel was associated with a HR for death of 0.78 (95%CI: 0.67-0.91).

The novelty of our finding is derived from our approach based on assessing efficacy of ARAT agents as a homogenous pharmacological class on the grounds of clinical and pharmacological data, which allowed to provide evidence supporting superior survival benefit compared to control of ARAT agents vs. docetaxel in the castration-sensitive setting via multiple analyses based on rigorous meta-analytic approach. Our analysis is limited by the retrospective design and definitive data can only be provided by a prospective comparison of monotherapy with docetaxel vs. an ARAT agent. Moreover, the results obtained with the network meta-analysis should be interpreted with caution, due to the limited number of available trials. Despite this caveat, we propose that an ARAT agent may be a more efficacious systemic treatment for unselected patients with mCSPC regardless of tumor volume. Furthermore, in patients with low volume CSPC, an ARAT agent may be combined with radiotherapy to the prostate[27]. However, a finite duration of therapy as offered by 6 cycles of docetaxel may still

be preferred by some patients with mCSPC. Further studies are warranted to identify subgroups potentially guided by molecular biomarkers (e.g. mutations in speckle-type pox virus and zinc finger protein gene[28]) who may derive greater OS benefit from docetaxel vs. an ARAT agent.

Conflicts of interest:

All other authors have no conflict to disclose

Table 1. Main characteristics of the trials and trial populations included in the quantitative meta-analysis.

RCT [reference]	Intervention arms	Main inclusion criteria	Number of patients	Age (median, IQR)	PFS (HR 95% CI)	OS (HR 95% CI)	Follow-up months (median, IQR)	Baseline PSA (median, IQR)	Visceral disease YES (n)	Visceral disease NO (n)	Gleason <8 (n)	Gleason >= 8 (n)	High volume (n)	Low volume (n)
LATITUDE [9]	ABIRATERONE plus ADT	Newly diagnosed castration-sensitive prostate cancer with metastases and no prior therapy. ECOG performance status of 0–2, and at least two of the three high-risk prognostic factors (Gleason score of ≥8, three or more lesions on bone scan, or measurable visceral metastasis except lymph node metastasis).	597	67.3	0.58 (0.49 - 0.68)	0.66 (0.57 - 0.78)	51.8 (47.2 - 57.0)	23.85 (range 0.0-8889.6) ng/ml	114	483	13	584	487	110
	PLACEBO plus ADT		602	66.8					114	488	16	586	468	133
TITAN [7]	APALUTAMIDE plus ADT	Castration-sensitive prostate cancer with metastases (at least one lesion on bone scanning, with or without visceral or lymph-node involvement). ECOG PS score of 0 or 1. Previous treatment for prostate cancer was limited to previous docetaxel use, ADT for no more than 6 months for metastatic or no more than 3 years for localized prostate cancer.	525	69 (45-94)	0.49 (0.39 - 0.62)	0.63 (0.47 - 0.85)	22.7	5.97 (range 0-2682) µg/l	56	469	174	351	325	200
	PLACEBO plus ADT		527	68 (43-90)				4.02 (range 0-2229) µg/l	72	455	169	358	335	192
ENZAMET [11]	ADT plus ENZALUTAMIDE	Castration-sensitive prostate cancer with metastases and ECOG score of 2 or less. Testosterone suppression was initiated up to 12 weeks before randomization. Previous adjuvant testosterone suppression for up to 24 months was allowed if the treatment had been completed at least 12 months earlier.	563	69.2 (63.2 - 74.5)	0.34 (0.26 - 0.44)	0.53 (0.37 - 0.75)	34	na	62	501	152	335	291	272
	ADT plus STANDARD NONSTEROIDAL THERAPY		562	69 (63.6 - 74.5)				na	67	495	163	321	297	263
STAMPEDE [21] [29]	ADT plus ABIRATERONE	Castration-sensitive prostate cancer with metastases, node-positive, or high-risk locally advanced (with at least two of following: a tumor stage of T3 or T4, a Gleason score of 8 to 10, and a PSA level ≥40 ng per milliliter) or disease that was previously treated with radical surgery or radiotherapy and was now relapsing with high-risk features.	501	67 (62-71)	0.45 (0.37 - 0.54)	0.60 (0.50 - 0.71)	73,2	96.3 (29-371) ng/ml	153	296	104	345	222	214
	ADT		502	67 (62-72)				97.2 (26-358) ng/ml	158	294	110	342	232	222

STAMPEDE[22][25]	ADT plus DOCETAXEL	Analyses of the M1 patient cohort treated with Docetaxel and with updated results using extended follow-up data to July 2018.	362	65 (62-70)	0.69 (0.59 - 0.81)	0.81 (0.69 - 0.95)	78.2 (62.9 – 96.3)	96.8 (37.8–348.1) ng/ml	126	216	65	253	148	124
	ADT		724	65 (60-71)				102.5 (33–338.7) ng/ml	268	410	158	480	320	238
CHAARTED [6]	DOCETAXEL plus ADT	Castration-sensitive prostate cancer with metastases and ECOG of 0, 1, or 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.	397	64 (36-88)	0.62 (0.51 - 0.75)	0.72 (0.59 - 0.89)	53,7	50.9 (range 0.2-8540.1) ng/ml	57	340	117	241	263	134
	ADT		393	63 (39-91)				52.1 (range 0.1-8056.0) ng/ml	66	327	104	243	250	143
GETUG-AFU 15 [23]	DOCETAXEL plus ADT	Castration-sensitive prostate cancer with metastases; Karnofsky score of at least 70%; life expectancy of at least 3 months; adequate hepatic, hematological, and renal function and no prior therapy.	192	63 (57-68)	0.67 (0.54 - 0.84)	0.88 (0.68 - 1.14)	83.9 (82.9 - 84.7)	26.7 (5.0-106.2) ng/ml	28	155	84	103	92	100
	ADT		193	64 (58-70)				25.8 (5.0-126.9) ng/ml	23	156	78	113	91	102

Table 2. Risk of bias according to the Cochrane Collaboration's tool.

ARTICLES	SELECTION BIAS		PERFORMANCE BIAS	DETECTION BIAS	ATTRITION BIAS	REPORTING BIAS	OTHER BIAS	TOTAL
	Random sequence generation	**Allocation concealment**	**Blinding of participants and personnel**	**Blinding of outcome assessment**	**Incomplete outcome data**	**Selective reporting**	**Anything else, ideally pre-specified**	**Low on risk of bias**
LATITUDE[9]	LOW	LOW	LOW	LOW	LOW	LOW	LOW	7/7
	Computer generated randomisation schedule	Central allocation	Blinded study	Blinded study	Adequate follow-up	No relevant data missing	The study appears to be free of other sources of bias.	
TITAN [7]	LOW	LOW	LOW	LOW	HIGH	LOW	LOW	6/7
	Central randomization system	Central allocation	Blinded study	Blinded study	Short follow-up	No relevant data missing	The study appears to be free of other sources of bias.	
ENZAMET[11]	LOW	LOW	HIGH	HIGH	HIGH	LOW	LOW	4/7
	Central randomization system	Central allocation	Open-label trial	Open-label trial	Short follow-up	No relevant data missing	The study appears to be free of other sources of bias.	
STAMPEDE[2	LOW	LOW	HIGH	HIGH	LOW	LOW	LOW	5/7

1] [29]	Central randomization system	Central allocation	Open-label trial	Open-label trial	Adequate follow-up	No relevant data missing	The study appears to be free of other sources of bias.	
STAMPEDE [22][25]	LOW	LOW	HIGH	HIGH	LOW	LOW	LOW	5/7
	Central randomization system	Central allocation	Open-label trial	Open-label trial	Adequate follow-up	No relevant data missing	The study appears to be free of other sources of bias.	
CHAARTED[6]	LOW	LOW	HIGH	HIGH	LOW	LOW	LOW	5/7
	Central randomization system	Central allocation	Open-label trial	Open-label trial	Adequate follow-up	No relevant data missing	The study appears to be free of other sources of bias.	
GETUG-AFU15[23]	LOW	LOW	HIGH	HIGH	LOW	LOW	LOW	5/7
	Central randomization system with dynamic minimisation	Central allocation	Open-label trial	Open-label trial	Adequate follow-up	No relevant data missing	The study appears to be free of other sources of bias.	

Figure 1. Flow chart of the systematic review.

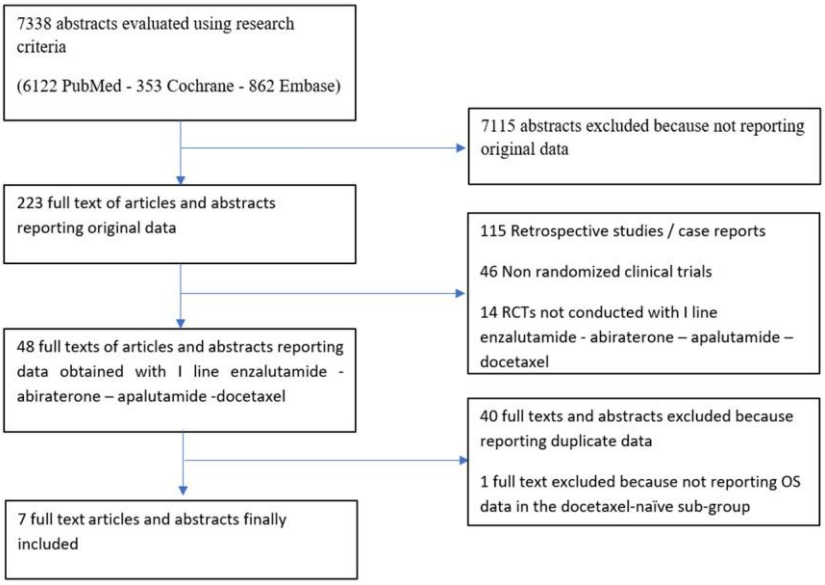


Figure 2. Pooled OS-HRs in ARAT and docetaxel randomized-controlled trials in the metastatic castration-sensitive setting

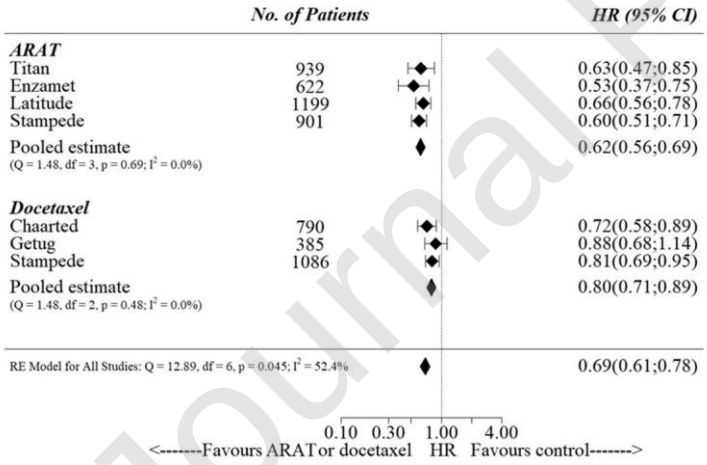


Figure 3. Network meta-analysis comparing ARAT vs. docetaxel

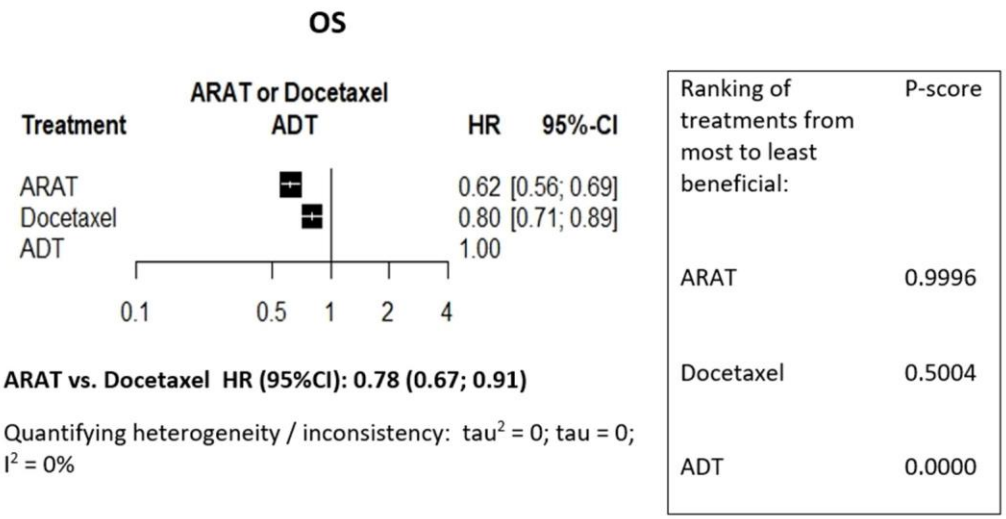
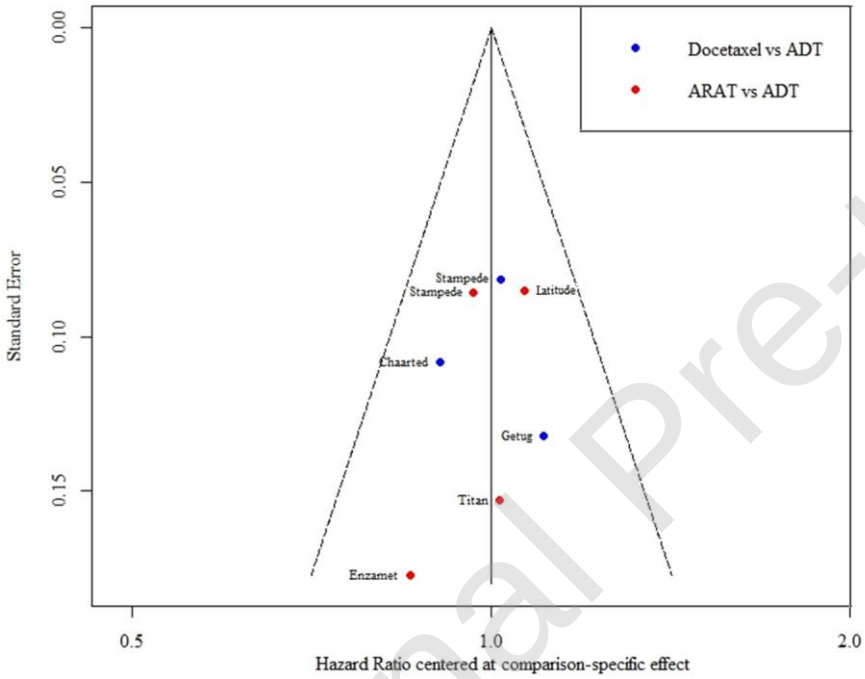


Figure 4. Funnel Plots of Hazard ratios for death



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Appendix 1. Search criteria

PUBMED	(((((((("prostatic neoplasms"[MeSH Terms] OR ("prostatic"[All Fields] AND "neoplasms"[All Fields])) OR "prostatic neoplasms"[All Fields]) OR ("prostatic"[All Fields] AND "cancer"[All Fields])) OR "prostatic cancer"[All Fields]) OR ((((("prostatic neoplasms"[MeSH Terms] OR ("prostatic"[All Fields] AND "neoplasms"[All Fields])) OR "prostatic neoplasms"[All Fields]) OR ("prostatic"[All Fields] AND "neoplasm"[All Fields])) OR "prostatic neoplasm"[All Fields])) AND ((((((((("metastatically"[All Fields] OR "metastatics"[All Fields]) OR "metastatization"[All Fields]) OR "metastatize"[All Fields]) OR "metastatized"[All Fields]) OR "metastatizing"[All Fields]) OR "secondary"[MeSH Subheading]) OR "secondary"[All Fields]) OR "metastatic"[All Fields])) AND ((((((((((("hormon"[All Fields] OR "hormonal"[All Fields]) OR "hormonally"[All Fields]) OR "hormonals"[All Fields]) OR "hormone s"[All Fields]) OR "hormones"[Pharmacological Action]) OR "hormones"[MeSH Terms]) OR "hormones"[All Fields]) OR "hormone"[All Fields]) OR "hormons"[All Fields]) AND (((((((((("hypersensitivity"[MeSH Terms] OR "hypersensitivity"[All Fields]) OR "sensitive"[All Fields]) OR "sensitively"[All Fields]) OR "sensitives"[All Fields]) OR "sensitivities"[All Fields]) OR "sensitivity and specificity"[MeSH Terms]) OR ("sensitivity"[All Fields] AND "specificity"[All Fields])) OR "sensitivity and specificity"[All Fields]) OR "sensitivity"[All Fields])))) OR ((((((((((("castrate"[All Fields] OR "castrated"[All Fields]) OR "castrates"[All Fields]) OR "castrating"[All Fields]) OR "castration"[MeSH Terms]) OR "castration"[All Fields]) OR "castrations"[All Fields]) OR "castrator"[All Fields]) OR "castrators"[All Fields]) OR "orchiectomy"[MeSH Terms]) OR "orchiectomy"[All Fields]) AND (((((((((("hypersensitivity"[MeSH Terms] OR "hypersensitivity"[All Fields]) OR "sensitive"[All Fields]) OR "sensitively"[All Fields]) OR "sensitives"[All Fields]) OR "sensitivities"[All Fields]) OR "sensitivity and specificity"[MeSH Terms]) OR ("sensitivity"[All Fields] AND "specificity"[All Fields])) OR "sensitivity and specificity"[All Fields]) OR "sensitivity"[All Fields]))
EMBASE	('prostatic cancer'/exp OR 'prostatic cancer' OR (prostatic AND ('cancer'/exp OR cancer)) OR 'prostatic neoplasm'/exp OR 'prostatic neoplasm' OR (prostatic AND ('neoplasm'/exp OR neoplasm))) AND metastatic AND ('hormone sensitive' OR (('hormone'/exp OR hormone) AND sensitive)) OR 'castration sensitive' OR (('castration'/exp OR castration) AND sensitive)
COCHRANE	((prostate cancer) OR (prostate neoplasm)) AND ((hormone sensitive) OR (castration sensitive))