Research Paper

Efficacy and safety of different interventions in castration resistant prostate cancer progressing after docetaxel-based chemotherapy: Bayesian network analysis of randomized controlled trials

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Abstract

Background: Most patients receiving docetaxel-based chemotherapy for castration resistant prostate cancer (CRPC) will eventually progress, and the optimal interventions for these patients are controversial. The objective of our study is to evaluate the clinical efficacy and safety of pharmacological interventions for CRPC patients progressing after docetaxel-based chemotherapy.

Methods: A systematic review and Bayesian network meta-analysis of the literature was carried out according to standard methods. Major electronic databases including PubMed, Web of Science and Embase were searched until Jan 2017. Hazard ratios (HRs) and odds ratios (ORs) with corresponding 95% credible intervals (CrIs) were used to estimate the association.

Results: 17 Randomized Controlled Trials (RCTs) comprising 14 different interventions with 12347 patients were enrolled. Compared with control arms, Abiraterone Acetate (HR: 0.70, 95%CrI: 0.63-0.79), Cabazitaxel (HR: 0.70, 95%CrI: 0.51-0.95) and Enzalutamide (HR: 0.63, 95%CrI: 0.53-0.75) presented similar benefits in term of OS. Enzalutamide showed superiority over PFS and PSA response with a highest probability to rank 1. Moreover, sensitivity analysis showed that Abiraterone Acetate (HR: 0.71, 95%CrI: 0.63-0.78) exhibited the most efficacious intervention of being rank 1 in term of OS compared with control arms, followed by Cabazitaxel and Cetuximab. On the other hand, Abiraterone Acetate (OR: 0.86, 95%CrI: 0.35-2.03) presented no significant toxicities compared with control arms.

Conclusions: Our results demonstrated that Abiraterone Acetate might be the optimal intervention for CRPC patients after docetaxel failure with acceptable tolerability. Future well-designed RCTs and systematic reviews are needed to validate these findings.

Key words: Castration resistant prostate cancer; Pharmacological Interventions; Docetaxel-based Chemotherapy; Bayesian network meta-analysis; Abiraterone Acetate; Enzalutamide

Introduction

Prostate cancer (PCa) is the second most commonly diagnosed cancer in the world, with 161,360 estimated new cases of PCa in 2017[1 2]. Less than 5% of patients present with metastatic disease,

up to 40% of detected cases will eventually develop metastasis [3]. Androgen deprivation therapy (ADT) has been the standard of care for metastatic PCa [4-6]. However, most patients eventually stop responding to ADT and are categorized as castration resistant prostate cancer (CRPC)[7], which is defined as either biochemically or clinically progressive metastatic disease despite castrate serum levels of testosterone (<50 ng/dL; <1.7nmol/L)[8]. After developing mCRPC, it is dismal with a median survival of 12 to 18 months[9].

Docetaxel is a standard first-line chemotherapy in men with CRPC based on improvements in overall survival (OS) and progression free survival (PFS), compared with Mitoxantrone plus prednisone [10] [11]. However, most of patients who receive docetaxel-based chemotherapy for mCRPC will eventually progress, and no consensus exist for the optimal interventions after docetaxel failure. The decision to initiate therapy demand the available high-level evidence of efficacy and tolerability in the post-docetaxel CRPC setting. Treatment options include Abiraterone with prednisone [12], Enzalutamide [13], Radium-223[14], Cabazitaxel[15] and so on. However, there are few randomized controlled trials (RCT) comparing different treatment strategies to inform patients regarding the comparative effectiveness of those interventions[16-18]. Therefore, pair-wise meta-analysis couldn't generate clear hierarchies among available treatments in this case, because they provide only partial information, and hence, do not optimally inform decision-making.

Network meta-analysis has been recently demonstrated to compare different interventions and integrate evidence from direct comparisons and indirect comparisons across a network of RCTs[19] [20]. Moreover, Bayesian network meta-analysis which synthesizes all evidence on the relative treatment effects, enables unified and coherent analysis of relevant RCTs[21]. Therefore, we applied the established methodology in the comprehensive network involving post-docetaxel treatments evaluating the clinical efficacy and tolerability of interventions for CRPC patients.

Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [22] [23].

Search strategy and selection criteria

We identified all relevant RCTs published from inception up to January 30, 2017 for assessing the clinical significance of currently available interventions for CRPC patients after docetaxel failure

from the following databases, including PubMed, EMBASE, MEDLINE, Web of Science, the Cochrane Library, Central Register of Controlled Trials. The MeSH terms were correctly adjusted in different database. The search strategy of PubMed is as follows: (("prostatic neoplasms"[MeSH Terms] OR ("prostatic" [All Fields] AND "neoplasms"[All Fields]) OR "prostatic neoplasms"[All Fields] OR ("prostate"[All Fields] AND "cancer"[All Fields]) OR "PCa"[All Fields]) AND ("orchiectomy"[MeSH Terms] OR "orchiectomy"[All Fields] OR "castration"[All Fields] OR "castration"[MeSH Terms]) AND resistant[All Fields] AND ("docetaxel"[MeSH Terms] OR "docetaxel-based chemotherapy" [All Fields] OR "taxane-based chemotherapy" [All Fields]) AND ("resistant" [All Fields] OR "failure" [All Fields] OR "refractory" [All Fields]) AND ("clinical trial" [Publication Type] OR "clinical trials as topic"[MeSH Terms] OR "clinical trial"[All Fields]). No language restrictions were applied. We also contacted the corresponding authors to acquire information if more information was needed.

Eligible studies in this network meta-analysis were RCTs that met the following inclusion criteria: (a) Patients: Histologically confirmed prostate cancer aged ≥18 years with castrate levels of serum testosterone (<50 ng/dL) were eligible if they had failed previous docetaxel-containing chemotherapy; documented progression was based on PSAWG criteria or radiographic progression in soft tissue or bone; (b) Intervention: established therapies for management of CRPC patients after docetaxel failure including chemotherapy, immunotherapy, androgen receptor targeting etc.; (c) Comparator: another active agent, Prednisone plus placebo, placebo, or no intervention; (d) Outcome: OS, PFS, PSA response and adverse events. We excluded observational studies, and trials comparing different doses of the same medication without an alternative intervention/comparator arm.

Data Extraction and quality assessment

Two authors (C.H. Chen and Y. Zhao) screened all the titles and abstracts identified by the search strategy independently, the results were assessed for eligibility. Disagreement was resolved by consensus between two authors or by a senior author (J. Huang). Data collection form was designed to collect information from these publications including first author, year of publication, follow-up, study type, participants, intervention and outcomes. We considered the OS, PFS and adverse events (Grade 3-4) for our primary analyses. Secondary outcome included PSA response (proportion of patients achieving ≥50% PSA decline according to PSAWG

criteria). Since randomized trials used low-dose oral daily corticosteroids in combination with mitoxantrone [24], they have been employed in combination with taxanes, with the rationale being to maintain balance between the arms [15 25]. However, the impact of prednisone on survival, as a single agent or in combination, remains unclear. Recently, comprehensive studies estimating the efficacy and safety with the use of daily prednisone indicated that Prednisone plus placebo arm showed similar benefit compared with placebo [26 27]. Thus, the reference standard was regarded as Prednisone plus placebo in the present study. For studies presenting the same RCT, we extracted the updated data for our meta-analysis, such as TROPIC trial reported by Bahl et al (2013)[28] and de Bono et al (2010)[15]. In order to evaluate the quality of including studies in this network meta-analysis, we assessed the risk of bias using the Cochrane Collaboration's Risk of Bias tool[29].

Statistical Analysis

We fitted a Bayesian network meta-analysis model for each outcome separately, combining direct evidence for each comparison with indirect evidence, for all pair-wise comparisons simultaneously. We evaluated inconsistency by comparing the estimates from direct comparisons and those from indirect comparisons for magnitude and direction of the point estimates. We estimated treatment effects by posterior means with corresponding 95% credible intervals (CrIs) and adjusted for different arms. Both the fixed and random effects models were applied. The differences between the two models were that the latter considers between-study variance, thereby producing wider CrIs, and was preferred in the presence of heterogeneity. Bayesian deviance information criterion (DIC) statistics were utilized to compare the two models. The DIC statistics provide a model fit measure which penalizes model complexity with lower values. We updated Markov chain Monte Carlo model with 100,000 simulated draws after a burn in of 10,000 iterations. The probability of each treatment being the best, second best, third best and so on, from the rank orderings of the treatments at each iteration of the Markov chain were recorded[30]. The network meta-analyses were built in WinBUGS (MRC Biostatistics Unit, Cambridge, UK) [20].

Pair-wise meta-analyses were conducted on endpoints. The traditional direct meta-analysis, two or more studies that compared two interventions of interest were statistically combined. The survival endpoints were expressed as hazard ratio (HR). Estimated survival curves for OS and PFS were plotted using the method described by Parmar et al[31].

The estimated hazard ratios of OS[32-35] and PFS[32 33 35] were obtained by using the above method. Dichotomous variables for PSA response and adverse events were presented as odds ratio (OR) with 95% confidence intervals (CIs). A two-sided *p* value of less than 0.05 was considered significant. The pair-wise meta-analysis was performed using Stata 13.0 (StataCorp, College Station, TX, USA).

Sensitivity analyses of the primary outcome would be applied in the RCTs which presented high-quality with control arm of Prednisone plus placebo. The threshold for good quality studies for sensitivity analysis was based on the Cochrane assessment tool for assessing the risk of bias. The studies with low risk of selection and flow bias were included. Publication bias was assessed by examining funnel plot symmetry and Egger's regression test [36].

Results

Search Results

From a total of 922 unique studies comparing all dfferent interventions identified using the search strategy, 17 RCTs composing of 14 interventions met the eligibility criteria for the current study. A flow chart of trial selection was shown in Figure 1. Eight RCTs of CRPC therapies were excluded because of unclear primary outcome assessment [37-41] and comparison of different dosing regimens without a common comparator group [42-44]. One study[45] presenting Mitoxantrone plus prednisone was excluded because it did not meet our inclusion criterion for data integration of control arms.

Table 1 summarized the main characteristics of RCTs included in the network meta-analysis. Overall, 12347 mCRPC patients with docetaxel failure were randomly enrolled to included studies. Median follow-up was 21 (range 12.8-36 months) and the sample size ranged from 82 to 1199 people, with a median sample size of 755. Based on the interventions under comparison, the included trials were classified into the following five categories, 1) Chemotherapy: Satraplatin, Cabazitaxel, Ixabepilone, Mitoxantrone; 2) Hormonal Strategies: Abiraterone acetate, Enzalutamide, Orteronel; 3) Target therapies: Sunitinib, Cetuximab, Rilotumumab, Cabozantinib; 4) Immune strategies: Siltuximab; 5) Bone-targeting agents: Ra-223. 17 trials provided OS, of which 11 trials reported PFS and 15 trials presented adverse events as primary endpoints for comparisons. 14 trials showed PSA response as secondary endpoint for comparisons.

Table 1. Characteristics of the studies included in the network meta-analysis

Study, Year of Publication; Identifier	Country; Inclusion Period	Follow-up median month, (95% CI)	Study type	Participants	Intervention	Outcomes
Bahl et al (2013)	Multi-center, Jan 2007-September 2009	25.5(20.7-30.0)	Phase III, Open label, RCT	1) Pathologically proven prostate cancer; 2) Surgical or hormone-induced castration; 3) Disease progression; 4) docetaxel failure	**Experimental**: Cabazitaxel + Prednisone **Control**: Mitoxantrone + Prednisone	OS,
de Bono et al (2010)	Multi-center, Jan 2007-Oct 2008	12.8(7.8-16.9)	Phase III, Open label, RCT	1) Pathologically proven prostate cancer; 2) Surgical or hormone-induced castration; 3) Disease progression; 4) docetaxel failure	**Experimental**: Cabazitaxel + Prednisone **Control**: Mitoxantrone + Prednisone	OS, PFS, PSA Response, Adverse event
de Bono et al (2011)	Multi-center, May 2008-Oct 2012	12.8	Phase III, Double blind, RCT	1) Pathologically proven prostate cancer; 2) Surgical or hormone-induced castration; 3) Disease progression; 4) Metastasis; 5) docetaxel failure	**Experimental**: Abiraterone acetate +Prednisone **Control**: Prednisone + Placebo	OS, PFS, PSA Response, Adverse event
Fizazi et al (1) (2012)	Multi-center, Nov 2006-Nov 2008	NA	Phase II, Open label, RCT	1) Pathologically proven prostate cancer; 2) Surgical or hormone-induced castration; 3) Disease progression; 4) Metastasis; 5) docetaxel failure	**Experimental**: Siltuximab + Mitoxantrone + Prednisone **Control**: Mitoxantrone + Prednisone	OS, PFS, PSA Response, Adverse event
Fizazi et al (2) (2012)	Multi-center, May 2008-Oct 2012	20.2(18.4-22.1)	Phase III, Double blind, RCT	1) Pathologically proven prostate cancer; 2) Surgical or hormone-induced castration; 3) Disease progression; 4) Metastasis; 5) docetaxel failure	**Experimental**: Abiraterone acetate +Prednisone **Control**: Prednisone + Placebo	OS, PSA response, Adverse event
Fizazi et al (2015)	Multi-center, Nov 2010-Sep 2014	NA	Phase III, Open label, RCT	1) Pathologically proven prostate cancer; 2) Surgical or hormone-induced castration; 3) Disease progression; 4) Metastasis; 5) docetaxel failure	**Experimental**: Orteronel + Prednisone **Control**: Prednisone + Placebo	OS, PFS, PSA Response, Adverse event
Fleming et al (2012)	Multi-center, May 2008-June 2011	30	Phase II, Open label, RCT	1) Pathologically proven prostate cancer; 2) Surgical or hormone-induced castration; 3) Disease progression; 4) Metastasis; 5) docetaxel failure	**Experimental**: Cetuximab + Mitoxantrone + Prednisone **Control**: Mitoxantrone + Prednisone	PFS, OS, PSA Response Adverse event
Hoskin et al (2014)	Multi-center, June 2008- Feb 2014	NA	Phase III, Double blind, RCT	1) Pathologically proven prostate cancer; 2) Surgical or hormone-induced castration; 3) Disease progression; 4) Bone metastasis; 5) docetaxel failure	**Experimental**: Radium-223 **Control**: Placebo	OS, Adverse event
Kantoff et al (1999)	Multi-center, Oct 1992-Sep 1995	NA	RCT	1) Pathologically proven prostate cancer; 2) Surgical or hormone-induced castration; 3) Disease progression; 4) docetaxel failure	**Experimental**: Mitoxantrone + Prednisone **Control**: Prednisone	OS, PFS, PSA Response, Adverse event
Michaelson et al (2014)	Multi-center, Jul 2008-Aug 2010	NA	Phase III, Double blind, RCT	1) Pathologically proven prostate cancer; 2) Surgical or hormone-induced castration; 3) Disease progression; 4) Metastasis; 5) docetaxel failure	**Experimental**: Sunitinib + Prednisone **Control**: Prednisone +Placebo	OS, PFS, PSA Response, Adverse event
Parker et al (2013)	Multi-center, Jan 2008-Feb 2011	36	Phase III, Double blind, RCT	1) Pathologically proven prostate cancer; 2) Surgical or hormone-induced castration; 3) Disease progression; 4) Bone metastasis; 5) docetaxel failure	**Experimental**: Radium-223 **Control**: Placebo	OS, Adverse event
Rosenberg et al (2007)	Multi-center, Feb 2003-Jun 2005	NA	Phase II, RCT	1) Pathologically proven prostate cancer; 2) Surgical or hormone-induced castration; 3) Disease progression; 4) docetaxel failure	**Experimental**: Ixabepilone **Control**: Mitoxantrone + Prednisone	OS, PSA Response, Adverse event
Ryan et al (2012)	Multi-center, Mar 2009-Dec 2009	21	Phase II, Double blind, RCT	1) Pathologically proven prostate cancer; 2) Surgical or hormone-induced	**Experimental One**: Rilotumumab (15 mg/kg) + Mitoxantrone + Prednisone	OS, PFS, PSA response,

Study, Year of Publication; Identifier	Country; Inclusion Period	Follow-up median month, (95% CI)	Study type	Participants	Intervention	Outcomes
				castration; 3) Disease progression; 4) Metastasis; 5) docetaxel failure	**Experimental Two**: Rilotumumab (7.5mg/kg) + Mitoxantrone + Prednisone **Control**: Mitoxantrone + Prednisone + Placebo	Adverse event
Scher et al (2012)	Multi-center, Sep 2009-Nov 2010	NA	Phase III, Double blind, RCT	1) Pathologically proven prostate cancer; 2) Surgical or hormone-induced castration; 3) Disease progression; 4) docetaxel failure	**Experimental**: Enzalutamide **Control**: Placebo	OS, PFS, PSA Response, Adverse event
Smith et al (2016)	Multi-center, Jul 2012-Nov 2014	NA	Phase III, Double blind, RCT	1) Pathologically proven prostate cancer; 2) Surgical or hormone-induced castration; 3) Disease progression; 4) Bone metastasis; 5) docetaxel failure	**Experimental**: cabozantinib **Control**: Prednisone	OS, PFS PSA Response
Sternberg et al (2009)	Multi-center, Sep 2003-Jan 2006	NA	Phase III, Double blind, RCT	1) Pathologically proven prostate cancer; 2) Surgical or hormone-induced castration; 3) Disease progression; 4) Bone metastasis; 5) docetaxel failure	**Experimental**: Satraplatin + Prednisone **Control**: Prednisone + Placebo	OS, PFS, PSA response, Adverse event
Sun et al (2016)	Multi-center, Aug 2012-June 2014	NA	Phase III, Double blind, RCT	1) Pathologically proven prostate cancer; 2) Surgical or hormone-induced castration; 3) Disease progression; 4) docetaxel failure	**Experimental**: Abiraterone acetate + prednisone **Control**: Prednisone + Placebo	OS, PSA Response, Adverse event

NA: not applicable; RCT: randomized controlled trial; OS: overall survival; PFS: progression free survival

Network meta-analysis outcomes

We established a network meta-analysis to compare the OS, PFS, PSA response and adverse event of different interventions. The respective sets of HRs and ORs with the corresponding 95% CrIs from the fixed effect model and random effect model had good consistency. The DIC values were lower in fixed effect model compared with random effect model for endpoints (range 5.36-10.07 vs range 5.57-88.68), indicating the fixed effect model had a substantially better fit than random effect model. Therefore, we applied the fixed effects model for the rest of the study. Supplementary Table 1 showed the summary of primary and secondary endpoints findings.

Efficacy results

A total number of 17 studies reported information of OS and 11 studies reported PFS were included in the present study. Figure 2 showed the full network diagram of eligible comparisons for OS, PFS and PSA response. In terms of OS, Abiraterone Acetate (HR: 0.70, 95%CrI: 0.63-0.79), Enzalutamide (HR: 0.63, 95%CrI: 0.53-0.75) and Cabazitaxel (HR: 0.70, 95%CrI: 0.51-0.95) were superior to control arms. Moreover, as hormonal strategies, both Abiraterone Acetate and Enzalutamide were significantly increasing OS than other interventions (Figure 3). In terms of PFS, Enzalutamide (HR: 0.40, 95%CrI: 0.35-0.46) was the most efficacious intervention with 87.9% cumulative probabilities of being rank 1 compared with control, followed by Cabozantinib and Abiraterone Acetate (Figure 4). In regards to PSA response, Abiraterone Acetate (OR: 6.25, 95%CrI: 2.27-20.0) and Enzalutamide (OR: 50.0, 95%CrI: 12.5-100.0) demonstrated significant benefits in terms of PSA response efficacy (Supplementary Figure 1).

Safety results

The network meta-analysis for adverse events (grade 3-4) was shown in Figure 3 and 4. Abiraterone Acetate (OR: 0.86, 95%CrI: 0.35-2.03) and Enzalutamide (OR: 1.22, 95%CrI: 0.31-5.60) presented no significant toxicities compared with control arms, whereas Mitoxantrone, Cabazitaxel, Ixabepilone, Cetuximab, Siltuximab and Rilotumumab were not as well tolerated compared with control arms for adverse events (grade 3-4).

Pair-wise meta-analysis outcomes

Results from pair-wise meta-analysis of including interventions were shown in Supplementary Figure 2, which were consistent with that of network meta-analysis. Pooled data showed that Abiraterone Acetate (HR: 0.70, 95%CI: 0.62-0.77), Enzalutamide (HR: 0.63, 95%CI: 0.52-0.74),

Cabazitaxel (HR: 0.71, 95%CI: 0.63-0.79) presented benefits compared with control in term of OS. Moreover, Abiraterone Acetate, Enzalutamide, Cabazitaxel and Orteronel were associated with longer PFS and higher PSA response than control arms.
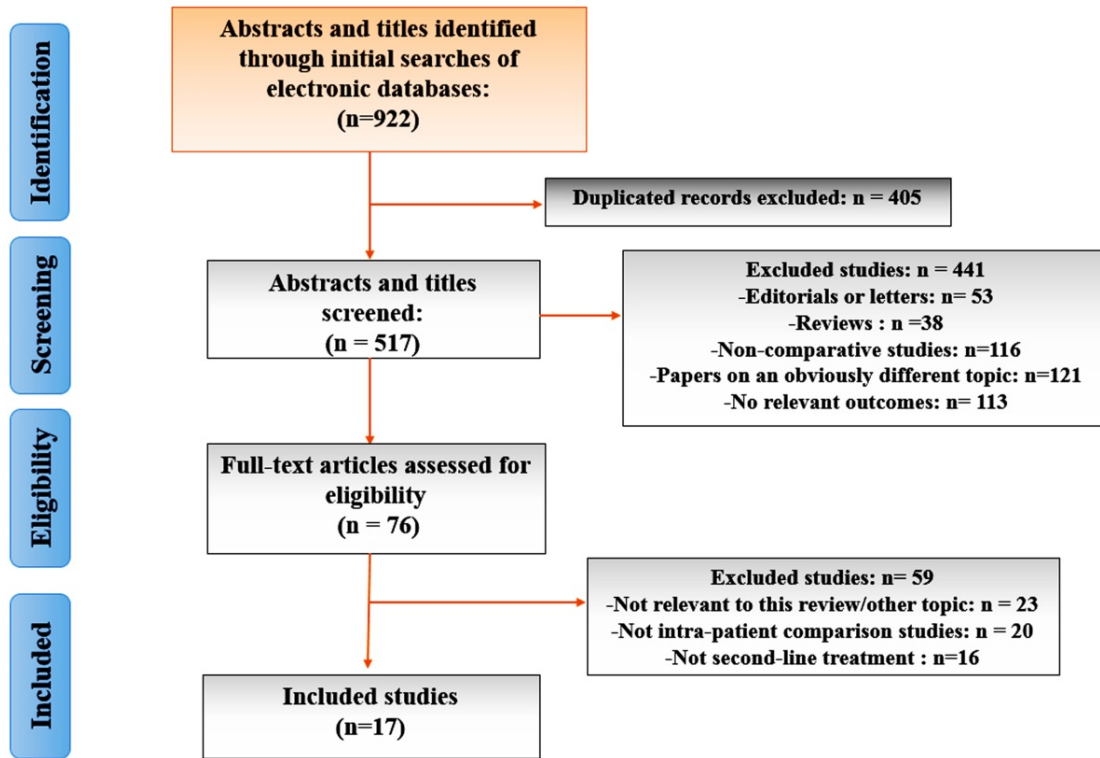

Figure 1. The PRISMA flow chart of included studies in network meta-analysis.
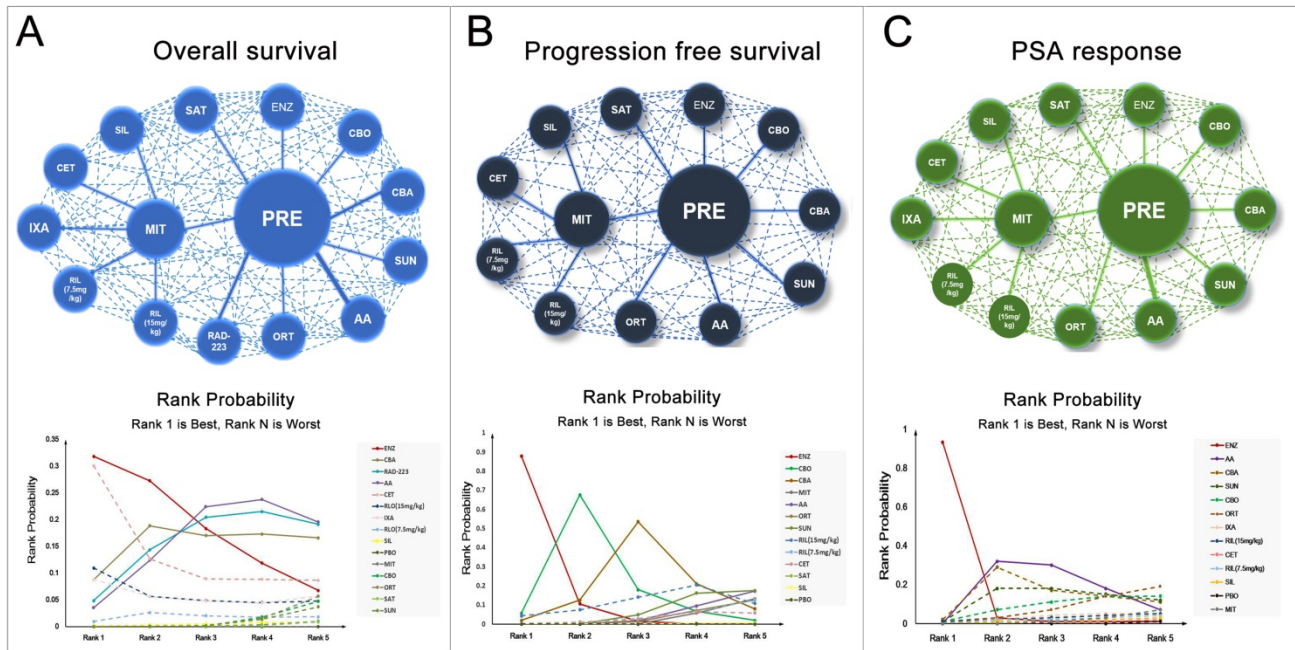

Figure 2. Network and rank probability of comparisons included in the analysis. Evidence network of different interventions for OS, PFS and PSA response for CRPC patients after docetaxel failure. The thickness of the connection line corresponds to the numbers of studies between comparators. Probabilities of each intervention ranking best, second, third, fourth and fifth best based on the fixed effects model. Full lines stand for agents with significant difference, while dash lines stand for agents without significant difference in comparisons.

	MIT	AA	CET	CBA	CBO	ENZ	IXA	ORT	RAD-223	PRE	SAT	SIL	SUN	RIL (15mg/kg)	RIL (7.5mg/kg)
MIT	MIT	**0.09 (0.02, 0.55)**	2.50 (0.55, 13.92)	2.45 (0.54, 10.73)	0.15 (0.02, 1.24)	**0.06 (0.01, 0.49)**	0.68 (0.13, 3.19)	0.14 (0.02, 1.16)	**0.06 (0.01, 0.46)**	**0.08 (0.02, 0.34)**	**0.07 (0.01, 0.62)**	1.07 (0.22, 4.85)	0.16 (0.02, 1.24)	1.89 (0.41, 9.20)	1.89 (0.41, 9.20)
AA	**0.72 (0.52, 0.97)**	AA	**28.32 (2.71, 309.42)**	**26.97 (2.79, 284.16)**	1.65 (0.29, 9.08)	0.70 (0.12, 3.71)	7.35 (0.72, 80.09)	1.61 (0.27, 8.52)	0.68 (0.12, 3.64)	0.86 (0.35, 2.03)	0.80 (0.16, 5.25)	**11.96 (1.12, 134.91)**	1.85 (0.30, 9.36)	**20.51 (2.26, 239.66)**	**20.51 (2.26, 239.66)**
CET	0.71 (0.41, 1.14)	1.01 (0.53, 1.74)	CET	0.97 (0.09, 8.06)	**0.06 (0.01, 0.75)**	**0.02 (0.01, 0.29)**	0.26 (0.03, 2.31)	**0.06 (0.01, 0.69)**	**0.02 (0.01, 0.29)**	**0.03 (0.01, 0.23)**	**0.03 (0.01, 0.36)**	0.42 (0.04, 3.84)	**0.07 (0.01, 0.71)**	0.75 (0.08, 7.06)	0.75 (0.08, 7.06)
CBA	**0.71 (0.63, 0.80)**	1.01 (0.71, 1.39)	1.05 (0.65, 1.68)	CBA	**0.06 (0.01, 0.88)**	**0.03 (0.01, 0.33)**	4.46 (0.31, 61.70)	**0.06 (0.01, 0.79)**	**0.02 (0.01, 0.34)**	**0.03 (0.01, 0.27)**	**0.03 (0.01, 0.44)**	0.43 (0.05, 4.00)	**0.07 (0.01, 0.96)**	0.76 (0.10, 7.68)	0.76 (0.10, 7.68)
CBO	0.93 (0.64, 1.27)	**1.29 (1.05, 1.56)**	1.37 (0.83, 2.34)	1.34 (0.92, 1.94)	CBO	0.42 (0.05, 3.25)	0.98 (0.13, 7.30)	0.05 (0.08, 3.08)	0.41 (0.05, 3.08)	0.53 (0.12, 2.24)	0.49 (0.06, 4.40)	7.39 (0.52, 99.21)	1.11 (0.14, 8.42)	**12.49 (1.06, 192.70)**	**12.49 (1.06, 192.70)**
ENZ	**0.65 (0.45, 0.9)**	0.90 (0.73, 1.11)	0.96 (0.58, 1.64)	0.94 (0.65, 1.36)	**0.7 (0.55, 0.89)**	ENZ	10.80 (0.81, 165.03)	2.30 (0.27, 19.01)	0.97 (0.14, 8.23)	1.22 (0.31, 5.60)	1.17 (0.16, 11.23)	**17.15 (1.24, 261.44)**	2.64 (0.33, 20.47)	**29.43 (2.51, 478.27)**	**29.43 (2.51, 478.27)**
IXA	0.99 (0.49, 1.78)	1.41 (0.63, 2.68)	1.46 (0.61, 3.00)	1.40 (0.69, 2.55)	1.09 (0.48, 2.07)	1.56 (0.68, 3.00)	IXA	0.21 (0.01, 2.85)	0.09 (0.01, 1.18)	**0.12 (0.01, 0.97)**	0.11 (0.01, 1.55)	1.62 (0.18, 14.83)	0.25 (0.02, 2.81)	2.90 (0.34, 26.80)	2.90 (0.34, 26.80)
ORT	0.91 (0.65, 1.24)	**1.27 (1.05, 1.52)**	1.35 (0.83, 2.3)	1.32 (0.93, 1.9)	0.99 (0.79, 1.22)	**1.42 (1.12, 1.77)**	0.99 (0.54, 1.77)	ORT	0.42 (0.06, 3.48)	0.53 (0.13, 2.50)	0.51 (0.07, 4.51)	7.47 (0.59, 104.75)	1.14 (0.12, 9.43)	**12.89 (1.07, 211.14)**	**12.89 (1.07, 211.14)**
RAD-223	**0.72 (0.51, 0.98)**	1.00 (0.83, 1.2)	1.06 (0.65, 1.79)	1.04 (0.73, 1.48)	**0.78 (0.63, 0.96)**	1.12 (0.88, 1.39)	0.78 (0.43, 1.38)	**0.79 (0.64, 0.97)**	RAD-223	1.27 (0.29, 5.64)	1.20 (0.14, 10.48)	**18.12 (1.30, 266.12)**	2.70 (0.33, 19.13)	**31.00 (2.48, 500.55)**	**31.00 (2.48, 500.55)**
PRE	1.01 (0.76, 1.37)	**1.43 (1.28, 1.59)**	1.43 (0.83, 2.63)	**1.43 (1.05, 1.96)**	1.11 (0.93, 1.32)	**1.59 (1.33, 1.89)**	1.02 (0.55, 2.22)	1.12 (0.98, 1.30)	**1.43 (1.25, 1.64)**	PRE	0.94 (0.22, 4.34)	**14.01 (1.51, 121.56)**	2.14 (0.47, 8.52)	**23.88 (3.28, 219.43)**	**23.88 (3.28, 219.43)**
SAT	1.01 (0.7, 1.39)	**1.40 (1.16, 1.96)**	1.49 (0.91, 2.55)	**1.47 (1.02, 2.11)**	1.10 (0.86, 1.36)	**1.57 (1.23, 2.00)**	1.09 (0.6, 1.94)	1.12 (0.9, 1.37)	**1.41 (1.14, 1.73)**	0.98 (0.83, 1.14)	SAT	**14.30 (1.00, 192.52)**	2.23 (0.26, 16.36)	**25.57 (2.23, 330.16)**	**25.57 (2.23, 330.16)**
SIL	1.53 (0.79, 2.7)	**2.15 (1.02, 4.04)**	2.25 (0.99, 4.5)	**2.16 (1.1, 3.86)**	1.68 (0.79, 3.18)	**2.4 (1.13, 4.59)**	1.65 (0.69, 3.34)	1.71 (0.81, 3.23)	**2.16 (1.03, 4.07)**	1.50 (0.73, 2.83)	1.55 (0.73, 2.95)	SIL	0.15 (0.01, 1.95)	1.73 (0.19, 18.05)	1.73 (0.19, 18.05)
SUN	0.94 (0.66, 1.3)	**1.31 (1.05, 1.62)**	1.39 (0.84, 2.42)	1.37 (0.94, 1.99)	1.03 (0.8, 1.29)	**1.47 (1.13, 1.89)**	1.02 (0.55, 1.82)	1.04 (0.83, 1.3)	**1.32 (1.05, 1.65)**	0.92 (0.77, 1.10)	0.94 (0.74, 1.19)	0.70 (0.38, 1.28)	SUN	**11.23 (1.07, 170.1)**	**11.23 (1.07, 170.1)**
RIL (15mg/kg)	1.07 (0.41, 2.28)	1.48 (0.58, 3.2)	1.55 (0.55, 3.68)	1.47 (0.59, 22.96)	1.14 (0.45, 2.45)	1.63 (0.63, 3.49)	1.13 (0.38, 2.7)	1.16 (0.45, 2.47)	1.47 (0.58, 3.12)	1.02 (0.41, 2.15)	0.95 (0.53, 2.08)	0.63 (2.29, 1.64)	1.02 (0.57, 2.27)	RIL (15mg/kg)	NA
RIL (7.5mg/kg)	1.42 (0.57, 3.03)	1.95 (0.78, 4.23)	2.06 (0.75, 4.91)	1.95 (0.82, 3.92)	1.52 (0.61, 3.26)	2.17 (0.86, 4.69)	1.50 (0.52, 3.72)	1.54 (0.62, 3.3)	1.95 (0.78, 4.17)	1.36 (0.55, 2.85)	1.09 (0.59, 2.22)	0.74 (0.34, 1.88)	1.18 (0.63, 3.3)	1.36 (0.81, 2.17)	RIL (7.5mg/kg)

Treatment   Overall survival (HR, 95%CrI)   Adverse events (OR, 95%CrI)

Figure 3. Pooled relative HRs for OS (pink region) and ORs for grade 3-4 adverse events (white region) based on mixed direct and indirect evidence from Bayesian network meta-analysis through fixed effects model with different pharmacological interventions in CRPC patients after docetaxel failure. The OS and safety estimates are located at the intersection of the column intervention and the row treatment (i.e., column intervention is reference for each comparison). To obtain HRs or ORs for comparisons in opposing direction, reciprocals should be applied. Results with statistic significant are in bold and underlined. Numbers in parentheses indicate 95% CrIs for network meta-analysis.

	MIT	AA	CET	CBA	CBO	ENZ	ORT	PRE	SAT	SIL	SUN	RIL (15mg/kg)	RIL (7.5mg/kg)
MIT	MIT	**0.09 (0.02, 0.55)**	2.50 (0.55, 13.92)	2.45 (0.54, 10.73)	0.15 (0.02, 1.24)	**0.06 (0.01, 0.49)**	0.14 (0.02, 1.16)	**0.08 (0.02, 0.34)**	**0.07 (0.01, 0.62)**	1.07 (0.22, 4.85)	0.16 (0.02, 1.24)	1.89 (0.41, 9.20)	1.89 (0.41, 9.20)
AA	0.97 (0.74, 1.24)	AA	**28.32 (2.71, 309.42)**	**26.97 (2.79, 284.16)**	1.65 (0.29, 9.08)	0.70 (0.12, 3.71)	1.61 (0.27, 8.52)	0.86 (0.35, 2.03)	0.80 (0.16, 5.25)	**11.96 (1.12, 134.91)**	1.85 (0.30, 9.36)	**20.51 (2.26, 239.66)**	**20.51 (2.26, 239.66)**
CET	1.19 (0.72, 1.83)	1.23 (0.69, 2.05)	CET	0.97 (0.09, 8.06)	**0.06 (0.01, 0.75)**	**0.02 (0.01, 0.29)**	**0.06 (0.01, 0.69)**	**0.03 (0.01, 0.23)**	**0.03 (0.01, 0.36)**	0.42 (0.04, 3.84)	**0.07 (0.01, 0.71)**	0.75 (0.08, 7.06)	0.75 (0.08, 7.06)
CBA	**0.74 (0.64, 0.86)**	0.76 (0.55, 1.04)	**0.63 (0.41, 0.93)**	CBA	**0.06 (0.01, 0.88)**	**0.03 (0.01, 0.33)**	**0.06 (0.01, 0.79)**	**0.03 (0.01, 0.27)**	**0.03 (0.01, 0.44)**	0.43 (0.05, 4.00)	**0.07 (0.01, 0.96)**	0.76 (0.10, 7.68)	0.76 (0.10, 7.68)
CBO	**0.63 (0.47, 0.83)**	**0.65 (0.52, 0.80)**	**0.53 (0.33, 0.82)**	0.85 (0.60, 1.18)	CBO	0.42 (0.05, 3.25)	0.98 (0.13, 7.30)	0.53 (0.12, 2.24)	0.49 (0.06, 4.40)	7.39 (0.52, 99.21)	1.11 (0.14, 8.42)	**12.49 (1.06, 192.70)**	**12.49 (1.06, 192.70)**
ENZ	**0.52 (0.40, 0.68)**	**0.54 (0.45, 0.65)**	**0.45 (0.28, 0.68)**	**0.71 (0.50, 0.97)**	0.83 (0.67, 1.03)	ENZ	2.30 (0.27, 19.01)	1.22 (0.31, 5.60)	1.17 (0.16, 11.23)	**17.15 (1.24, 261.44)**	2.64 (0.33, 20.47)	**29.43 (2.51, 478.27)**	**29.43 (2.51, 478.27)**
ORT	1.00 (0.76, 1.29)	1.03 (0.84, 1.24)	0.85 (0.53, 1.29)	1.35 (0.95, 1.86)	**1.59 (1.26, 1.98)**	**1.91 (1.54, 2.35)**	ORT	0.53 (0.13, 2.50)	0.51 (0.07, 4.51)	7.47 (0.59, 104.75)	1.14 (0.12, 9.43)	**12.89 (1.07, 211.14)**	**12.89 (1.07, 211.14)**
PRE	**1.33 (1.02, 1.69)**	**1.35 (1.20, 1.53)**	1.10 (0.66, 1.89)	**1.75 (1.33, 2.33)**	**2.08 (1.75, 2.50)**	**2.5 (2.17, 2.86)**	**1.32 (1.12, 1.54)**	PRE	0.94 (0.22, 4.34)	**14.01 (1.51, 121.56)**	2.14 (0.47, 8.52)	**23.88 (3.28, 219.43)**	**23.88 (3.28, 219.43)**
SAT	1.5 (0.83, 2.56)	1.18 (0.63, 2.05)	0.97 (0.48, 176)	1.55 (0.88, 2.59)	1.82 (0.97, 3.16)	**2.19 (1.16, 3.82)**	1.15 (0.61, 2.00)	1.00 (0.85, 1.16)	SAT	**14.30 (1.00, 192.52)**	2.23 (0.26, 16.36)	**25.57 (2.23, 330.16)**	**25.57 (2.23, 330.16)**
SIL	1.21 (0.66, 2.09)	0.95 (0.50, 1.66)	0.78 (0.38, 1.43)	1.25 (0.70, 2.10)	1.47 (0.76, 2.55)	1.77 (0.92, 3.14)	0.93 (0.48, 1.63)	1.36 (0.71, 2.35)	1.44 (0.85, 2.36)	SIL	0.15 (0.01, 1.95)	1.73 (0.19, 18.05)	1.73 (0.19, 18.05)
SUN	1.31 (0.98, 1.7)	**1.35 (1.11, 1.65)**	1.11 (0.70, 1.71)	**1.78 (1.26, 2.45)**	**2.08 (1.65, 2.60)**	**2.5 (2.01, 3.07)**	**1.32 (1.06, 1.62)**	**0.73 (0.60, 0.89)**	0.73 (0.56, 0.92)	0.54 (0.30, 0.94)	SUN	**11.23 (1.07, 170.16)**	**11.23 (1.07, 170.16)**
RIL (15mg/kg)	**1.78 (1.00, 2.94)**	1.84 (0.95, 3.22)	1.51 (0.73, 2.81)	**2.41 (1.32, 4.04)**	**2.83 (1.45, 4.99)**	**3.41 (1.74, 6.00)**	**1.79 (0.91, 3.12)**	0.88 (0.48, 1.50)	0.91 (0.55, 1.69)	0.66 (0.35, 1.47)	1.25 (0.77, 2.33)	RIL (15mg/kg)	NA
RIL (7.5mg/kg)	0.95 (0.70, 1.27)	0.98 (0.78, 1.24)	0.81 (0.50, 1.27)	1.29 (0.90, 1.80)	**1.51 (1.17, 1.95)**	**1.82 (1.42, 2.31)**	0.96 (0.75, 1.22)	0.71 (0.37, 1.21)	0.69 (0.53, 1.18)	0.51 (0.27, 1.11)	0.95 (0.58, 1.67)	0.80 (0.52, 1.19)	RIL (7.5mg/kg)

Treatment   Progression free survival (HR, 95%CrI)   Adverse events (OR, 95%CrI)

Figure 4. Pooled relative HRs for PFS (green region) and ORs for grade 3-4 adverse events (white region) based on mixed direct and indirect evidence from Bayesian network meta-analysis through fixed effects model with different pharmacological interventions in CRPC patients after docetaxel failure. The PFS and safety estimates are located at the intersection of the column intervention and the row treatment (i.e., column intervention is reference for each comparison). To obtain HRs or ORs for comparisons in opposing direction, reciprocals should be applied. Results with statistic significant are in bold and underlined. Numbers in parentheses indicate 95% CrIs for network meta-analysis.
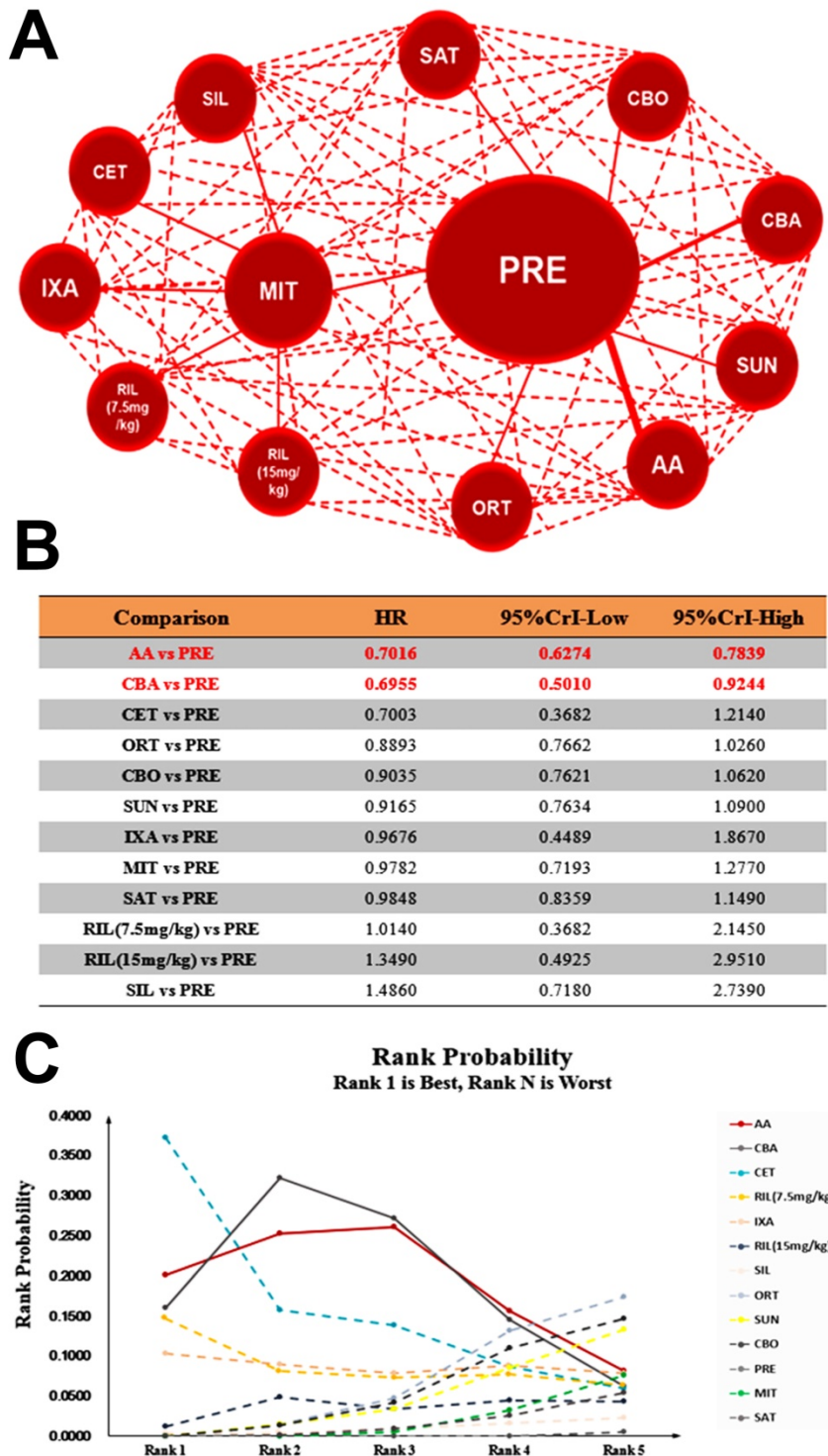
Figure 5. The network meta-analysis outcomes of eligible comparisons of OS excluding studies with control arm of placebo: network diagram (A), relative HRs (B) and rank probability (C) based on mixed direct and indirect evidence from Bayesian network meta-analysis through fixed effects model with different pharmacological interventions in CRPC patients after docetaxel failure.

Comparison	HR	95%CrI-Low	95%CrI-High
AA vs PRE	0.7016	0.6274	0.7839
CBA vs PRE	0.6955	0.5010	0.9244
CET vs PRE	0.7003	0.3682	1.2140
ORT vs PRE	0.8893	0.7662	1.0260
CBO vs PRE	0.9035	0.7621	1.0620
SUN vs PRE	0.9165	0.7634	1.0900
IXA vs PRE	0.9676	0.4489	1.8670
MIT vs PRE	0.9782	0.7193	1.2770
SAT vs PRE	0.9848	0.8359	1.1490
RIL(7.5mg/kg) vs PRE	1.0140	0.3682	2.1450
RIL(15mg/kg) vs PRE	1.3490	0.4925	2.9510
SIL vs PRE	1.4860	0.7180	2.7390

Sensitivity analysis

Theoretically daily low dose corticosteroids appear to have modest antitumor activity and may avert adverse effects of other antitumor agents[12], we performed further pooled analysis including studies with control arm of Prednisone plus placebo. Our results showed that Abiraterone Acetate (HR: 0.71, 95%CrI: 0.63-0.78) was the most efficacious intervention of being rank 1 in OS compared with Prednisone plus placebo followed by Cabazitaxel and Cetuximab, when Enzalutamide and Radium-223 were excluded for control arm of placebo (Figure 5).

In terms of PFS, Abiraterone Acetate (HR: 0.74, 95%CrI: 0.66-0.83) also presented the most efficacious intervention of being rank 1 (Supplementary Figure 3). In regards to PSA response, Abiraterone Acetate showed significant superiority over control arm (OR: 6.17, 95%CrI: 2.83-13.59) (Supplementary Figure 4). Together, our results suggest that Abiraterone Acetate might be the efficacious intervention compared with control arm in terms of OS, PFS and PSA Response.

Risk of bias assessment

The risk of bias of included studies was reported in Figure 6. In fact, none of the trials were thought to have a high risk of bias for any of the methodological quality items assessed. In summary, 13 (76%) of the 17 trials reported an adequate method of allocation concealment and 14 (82%) of the 17 trials reported low risk method for blinding of outcomes. We did not find evidence of publication bias in OS, PSA response and adverse event, based on funnel plot asymmetry or quantitatively (Egger's regression test p=0.266, 0.178 and 0.084), while Egger's regression test in PFS showed statistical significance (p=0.038) (Supplementary Figure 5).

Discussion

This systematic review and network meta-analysis represents the most comprehensive synthesis of data for currently available pharmacological interventions for patients with mCRPC who had progressed after docetaxel-based chemotherapy. 17 RCTs with 12347 enrolled patients were included in this network meta-analysis. The main new finding is that Abiraterone Acetate, Cabazitaxel and Enzalutamide presented better benefits in term of OS compared with control arms. Enzalutamide demonstrated superiority over PFS and PSA response with a highest probability to rank 1. Moreover, sensitivity analysis showed that Abiraterone Acetate exhibited the most efficacious intervention of being rank 1 in term of OS compared with control, followed by Cabazitaxel and Cetuximab. In regards to PFS, Abiraterone Acetate also presented the most efficacious intervention of being rank 1. Together, our results suggested that Abiraterone Acetate might be the efficacious intervention compared with control arms for mCRPC patients progressing after docetaxel-based chemotherapy.

Previously, post-docetaxel treatment options for mCRPC were limited, with few benefits observed in terms of OS. Since 2010, we have witnessed unprecedented therapeutic advances in treatment after prior docetaxel-based chemotherapy for men with mCRPC, including Cabazitaxel (tubulin-binding taxane)[15 28] approved by the FDA in 2010, Abiraterone Acetate (androgen biosynthesis inhibitor)[12 46 47] approved by the FDA in 2011 and Enzalutamide (androgen receptor antagonist)[13 38 48-50] approved by the FDA in 2012. All of the regimens have been demonstrated to improve efficacy and have become parts of the therapeutic arsenals mCRPC after docetaxel failure. An important finding within the present study is that, Abiraterone Acetate appears to be efficacious treatment option for mCRPC patients after docetaxel failure because of the higher efficacy and lower adverse events. Abiraterone Acetate, a steroidal drug, inhibits CYP17A1, blocks androgen synthesis decreasing the intracellular testosterone level and prolong survival before or after docetaxel chemotherapy, recent study has indicated the metabolites of Abiraterone Acetate showed antagonistic effect on androgen receptor [12 47 51]. It might partially explain the outcomes in our study.

Entering this new therapeutic era in oncology, numbers of mechanistic drug classifications have produced a more diverse range of potential toxicities. CTCAE is a standard evaluating system designed to assess symptomatic toxicities and provide additional tolerability data [52]. The interventions included in our study composed of chemotherapy, hormonal strategies, antiangiogenic therapies, immune strategies and bone-targeting agents, and the assessments of severe adverse events (Grade 3-4) could better inform us the tolerability information of the therapies. Our results indicated reported adverse events of hormone strategies were less severe than cytotoxic agents, and were manageable by appropriate patient monitoring. The novel androgen receptor targeting agents (Abiraterone Acetate and Enzalutamide) presented similar severe adverse events with control arms, which could be better tolerated than cytotoxic therapies.

To the best of our knowledge, this study is the first network meta-analysis to assess the efficacy and safety of different interventions for post-docetaxel therapy in mCRPC patients. We overcame the difficulties of different measures of survival across studies and synthesized all available studies within a single network meta-analysis, avoiding potential selection bias in the meantime. This network meta-analysis provides new insights into controversies on this issue with important implications in clinical care and future research. However, this study also has limitation. We extracted all information from published data rather than original individual patient data, which may lead to publication and reporting bias and missing information on certain endpoints might affected our analysis without access to individual patient data. We minimized the risk of bias through searching and

reviewing the publications comprehensively, and extracting and evaluating the data systematically, we also performed further pooled analysis excluding agents with control arm of placebo for theoretical reasons. Moreover, our findings are the results of direct and indirect comparisons in a network meta-analysis. Although this method is widely accepted, it does not substitute results from RCTs. Future systematic reviews are needed to assess the efficacy and safety of these interventions by identifying those patients who most benefit.
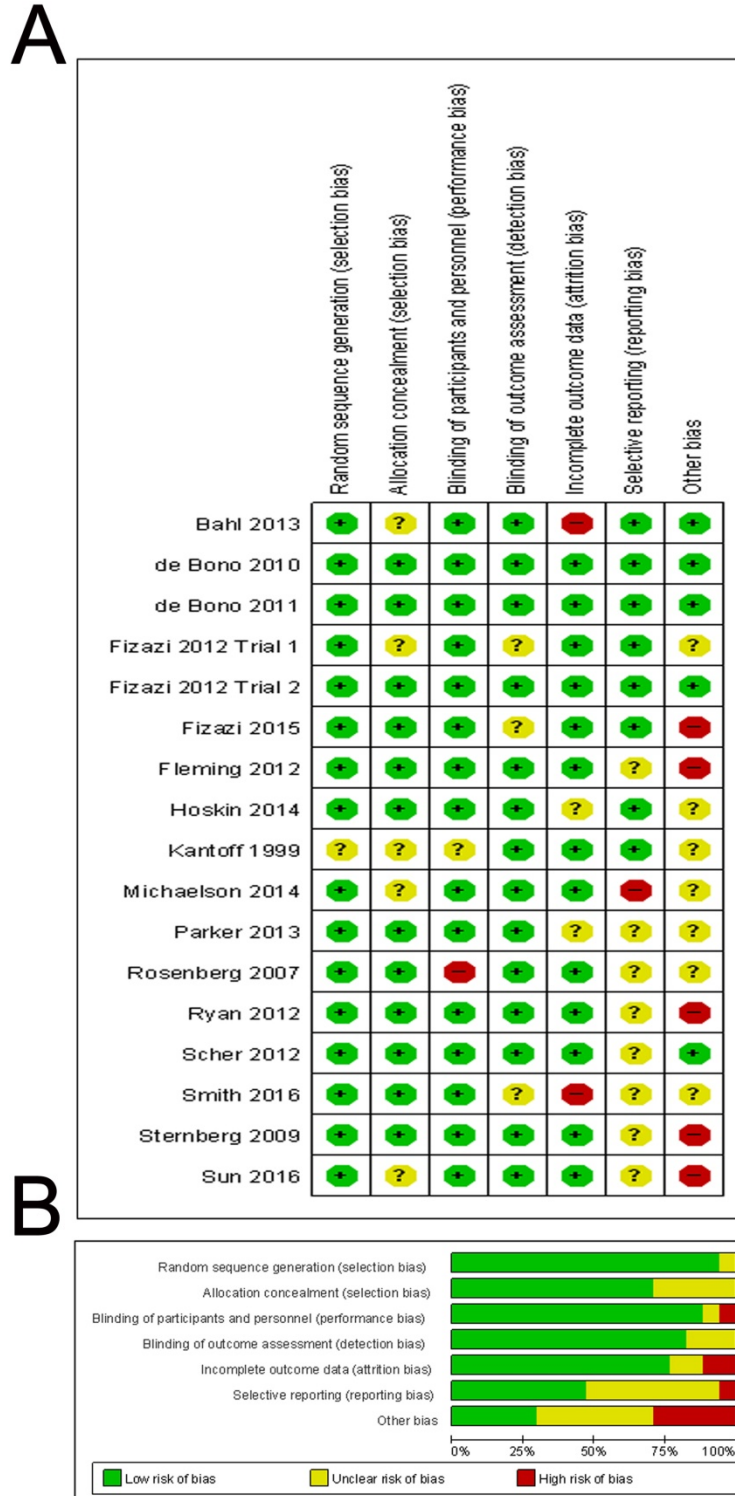
Figure 6. Quality assessment of included studies. The Overall (A) and Study-level distribution plot for risk of bias using Cochrane's risk of bias assessment tool. Studies are deemed to be at high, low or unclear risk of bias for each risk of bias entry. The review authors' judgments about each risk of bias entry are presented as percentages across all included studies.

Conclusions

In conclusion, our network meta-analysis demonstrated that Abiraterone Acetate, Cabazitaxel and Enzalutamide were associated with favorable OS when compared with control arms. Abiraterone Acetate appears to be efficacious treatment option for mCRPC patients after docetaxel failure because of the higher efficacy and lower adverse events. Similar observations were also noted for PFS and PSA response. Further sensitivity analysis indicated Abiraterone Acetate showed significant benefit in prolonging survival. Future well-designed RCTs and systematic reviews are awaited to confirm the findings of this study.

Clinical Practice Points

- The consensus is not existing of optimal strategies for CRPC patients after docetaxel failure. Several randomized trials were conducted to investigate efficacy and safety of interventions.

- This network meta-analysis showed for the first time that Abiraterone Acetate (HR: 0.71, 95%CrI: 0.63-0.78) exhibited the most efficacious intervention of being rank 1 in term of OS compared with control arms.

- The analysis of 17 randomized trials provides evidence in favor of Abiraterone Acetate for CRPC patients after docetaxel failure with acceptable tolerability and good performance status.

Abbreviations

PCa: Prostate cancer; ADT: Androgen deprivation therapy; CRPC: Castration Resistant Prostate Cancer; OS: Overall Survival; PFS: Progression Fee Survival; RCT: Randomized Controlled Trials; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses; HR: Hazard Ratio; OR: Odds Ratio; CrIs: Credible Intervals; DIC: Deviance Information Criterion; CTCAE: Common Terminology Criteria for Adverse Events; EAU: European Association of Urology; NCCN: National Comprehensive Cancer Network; MIT: Mitoxantrone; CBA: Cabazitaxel; PRE: Prednisone plus Placebo; AA: Abiraterone acetate; SIL: Siltuximab; ORT: Orteronel; CET: Cetuximab; RAD: Radium-223; SUN: Sunitinib; IXA: Ixabepilone; RIL: Rilotumumab; ENZ: Enzalutamide; CBO: Cabozantinib; SAT: Satraplatin.

Supplementary Material

Supplementary figures and tables.
http://www.jcancer.org/v09p0690s1.pdf

Competing Interests

The authors have declared that no competing interest exists.

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