Efficacy and safety of novel treatments in chemotherapy-naïve castration-resistant prostate cancer

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Research article

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Abstract

Background: Currently, novel treatment methods for chemotherapy-naïve castration-resistant prostate cancer (CRPC) patients have been applied in clinical practice. Since the optimum regimen remains inconclusive, this study compares the efficacy and safety of these treatments by network meta-analysis.

Methods: The PubMed and ClinicalTrials.gov database and review articles before January 30, 2020 were searched and date were extracted. A total of 29908 patients with CRPC from 23 randomized controlled trials were included. Relative hazard ratios (HR) had been used to assess the effects on overall survival (OS), progression-free survival (PFS) or radiographic PFS (rPFS), and adverse events (AEs). We then pooled the data and used Bayesian and frequentist random-effects model to identify the best treatment strategy.

Results: Compared with the placebo, both Bayesian and frequentist random-effects network meta-analyses found that only enzalutamide and abiraterone had a significant effect in OS. Similar results were observed in PFS/rPFS. Bicalutamide, tasquinimod and orteronel could also improve rPFS. Enzalutamide only could improve rPFS more effectively than abiraterone with no significant differences in OS/PFS/AEs. In any subgroups of patients with age <75, ≥75 or ECOG score = 0,1 or Gleason score ≤7, ≥8, enzalutamide could improve the OS significantly. Nevertheless, the significant benefit of abiraterone was only found in patients with age <75 and ECOG score = 0.

Conclusions: Our network analysis suggested that both enzalutamide and abiraterone are optimal treatment for chemotherapy-naïve CRPC patients with age <75 and ECOG score = 0 for great improvement on OS and PFS. In addition, enzalutamide is also an optimum therapy for chemotherapy-naïve CRPC patients with age ≥75 and ECOG score = 1.

Background

Prostate cancer (PCa) is one of the most common cancers and cause of cancer-related deaths in older men.[1] Most of the patients are initially sensitive to androgen depletion therapy (ADT), but they eventually progress to castration-resistant prostate cancer (CRPC).[2] In 2004, docetaxel was approved by the FDA as first-line chemotherapy to treat CRPC patients based on their improved survival.[3] Similarly, the progression of the disease was inevitable, and docetaxel was associated with significant toxicity, high cost, and modest benefits.[4, 5] As a result, novel therapies were explored to improve the survival and delay the chemotherapy in order to avoid the associated toxicity.[6] The wide use of docetaxel in CRPC created three novel treatment options: pre-docetaxel, combination with docetaxel, and post-docetaxel. [7, 8]

Due to the expanding knowledge in understanding the molecular pathways involved in CRPC progression, many new therapeutic agents have been tested as second-line therapy in CRPC patients in the form of randomized controlled trials (RCTs).[9] Despite resistance to initial ADT, most patients respond to second-line new therapies in recent years, such as androgen receptor antagonist. [10]

However, second-line therapy decisions in chemotherapy-naive patients are challenging because CRPC is a heterogeneous disease, and only a few RCTs directly compared these new agents.[11] In addition, some agents were tested in pre-docetaxel setting and some in combination with docetaxel.[12,13] It is one of the reasons that the American Society of Clinical Oncology (ASCO) guidelines does not directly address the second line therapy in the chemotherapy-naive patients, but it can address the use of systemic chemotherapy in metastatic CRPC.[14] Thus, managing CRPC patients, especially chemotherapy-naïve patients in clinician settings is rather challenging. For instance, should chemotherapy-naïve CRPC patients use second-line new therapeutic agents and which one of them is optimal? As only a few RCTs with direct comparative data and evidence are available for these novel agents, treatment patterns for chemotherapy-naïve CRPC patients remain controversial.

Therefore, the present study aimed to review the recent RCTs in chemotherapy-naïve CRPC patients by comparing the novel second-line treatments and investigating their efficacy and safety in these patients through a network meta-analysis approach. Network meta-analysis can overcome the limitations of the direct comparisons of novel agents. In addition, it can synthesize the results of all the relative comparisons to achieve accurate statistical results that have not been compared directly by any RCTs.[15,16] Therefore, we summarized the direct and indirect effects in different second-line therapies, provided evidence, and derived a precise estimation on the treatment decisions in chemotherapy-naïve CRPC patients.

Methods

Search strategies and selection criteria

PubMed, Embase, and ClinicalTrials.gov databases were searched until January 30, 2020, by two authors using the following keywords: “castration-resistant prostate cancer” and “randomized controlled trial” or “RCT.” The publication languages and years were not restricted in this search. Abstracts and virtual meeting presentations in the last 10 years were also searched to identify the relevant clinical trials. Reference lists in the original articles and review articles were also examined for additional trials.

Trials were eligible if they investigated the efficacy and safety of novel agents in chemotherapy-naïve CRPC patients. For inclusion in the current study, the identified articles had to provide the following: (1) information on the evaluation of overall survival (OS), progression-free survival (PFS), or safety; (2) sufficient published data for evaluating the overall hazard ratios (HRs) with 95% confidence intervals (CIs); (3) case-control design; (4) chemotherapy-naïve CRPC patients. The exclusion criteria were as follows: (1) no usable data reported; (2) duplicate data. We initially screened the titles and abstracts to exclude studies that did not meet the above inclusion criteria. Subsequently, two authors independently screened full texts for the inclusion of data in the current study.

Data extraction and quality assessment

Data were independently extracted from each report, using a standardized data recording form. The risk of bias in individual studies was assessed using the Cochrane risk-of-bias method. The risk of bias encompasses 7 domains, including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

Data synthesis and analysis

The primary outcome measure was overall survival, and the secondary outcome measures were PFS/rPFS and adverse events (AEs). If more than one related outcome was reported, the latest one was selected. In the subgroup analysis, if more than three studies reported similar variables (such as age, ECOG, Gleason), a network analysis was carried out. As HR provides time-to-event information and confounders have been adjusted, the HR for OS, PFS/fPFS, and odds ratios (ORs) for different types of AEs were analyzed. HR <1 indicates deaths or progression in the placebo arm, and OR <1 indicates toxicities in the placebo arm and vice versa. To minimize the impact of heterogeneity, random-effects models were used for analysis. Both Bayesian network meta-analyses and frequentist network meta-analyses were conducted.

A network plot was made to represent the overall information of studies included in the current study. Node size represents the number of studies for each treatment, and lines thickness represents the number of available direct comparisons. P-score, based on the point estimates, was used for comparing the treatments in a network meta-analysis. P-scores were calculated and induce a ranking of all treatments.[17] A forest plot was constructed by network meta-analysis with placebo as the baseline regimen. Inconsistency was defined as the disagreement between direct and indirect therapy comparisons and was detected by network meta-analysis. R (R i386 3.4.2) and JAGS (JAGS 4.2.0) were utilized for Bayesian network meta-analysis. Frequentist network meta-analysis was conducted by R and STATA 14.0 (Stata Corp, College Station, TX, USA).

Results

A total of 394 articles were retrieved originally after the electronic literature search. After screening the titles and abstracts, 303 articles were excluded resulting in 91 articles that were potentially relevant for inclusion into the study. An additional 68 articles were excluded from 91 articles for the following reasons: duplicate date, preliminary meeting reports, and not reported/could not obtain usable data that can help infer the results in the current article. As a result, 23 RCTs with 29908 patients that fulfilled the inclusion criteria were identified. (Fig A.1) Among these, 19 trials were phase III, and 4 trials were phase II RCTs. The baseline characteristics are listed in Table A.1. In addition, 7 trials investigated the role of new agents in combination with docetaxel in chemotherapy-naive CRPC patients. The study (MP Wirth (2004)) included 3 trials, and hence, we calculated it as 3 independent trials in our analysis. All trials were reported in full-text and most of trials had a low risk of bias (Fig A.2).[5, 7-13, 18-32]

In the OS analysis, 22 trials were included. Of these, 7 investigated the new agents combined with docetaxel, and 15 trials investigated the new agents alone. Figure 1A shows the relative comparisons analyzed in the network. HR and the 95% CI were explicitly reported in all the published articles. Compared to the placebo, both random-effects Bayesian and frequentist network meta-analyses found that only enzalutamide (HR=0.71, 95% CI: 0.52–0.95, HR=0.71, 95% CI: 0.52–0.95, respectively) and abiraterone (HR=0.73, 95% CI: 0.58–0.89, HR=0.73, 95% CI: 0.62–0.85, respectively) had a significant impact on OS (Figure 2A). In addition, the results of two frame networks were similar. Combined with the convergent and lever graph, the network showed consistent results (Fig A.3). Although none of the trials compared the efficacy between enzalutamide and abiraterone, we used our network to explore the comparison. As shown in Figure 2A, the indirect comparison of HR was 0.99 (95% CI: 0.72–1.40) with no significance. Similarly, no significant outcome was detected in Bayesian and frequentist frame network meta-analysis comparing enzalutamide and abiraterone (HR=0.97, 95% CI: 0.68–1.40, HR=0.98, 95% CI: 0.74–1.30, respectively); the P-value in both treatments were similar.

In the subgroup analysis, only 3 articles analyzed the subgroup of age (<75, ≥75), ECOG score (0,1), and Gleason score (≤7, ≥8), respectively. Therefore, a network was created in these subgroups, which provided interesting results. As shown in Figure 3, both enzalutamide and abiraterone had significant improvements in the OS in patients with age <75 years. However, only enzalutamide had the same trend in patients with age ≥75 years. Similar results were observed in the ECOG score subgroup, and the P-scores of enzalutamide were higher than abiraterone in all comparisons. In the Gleason score subgroup, only enzalutamide, ipilimumab, and orteronel were investigated for efficacy without abiraterone. The results indicated that enzalutamide could improve the OS significantly in both Gleason ≤7 and Gleason ≥8 subgroups.

All new agents in combination with docetaxel did not show any significant improvements in the OS in network meta-analysis when compared to the placebo and docetaxel (Fig A.4A). The results also indicated that chemotherapy-naïve CRPC patients had to postpone the initiation of cytotoxic chemotherapy. For the median time to the initiation of cytotoxic chemotherapy and the median time to decline of the FACT-P global score, there were 5 and 4 novel agents, respectively, involved in the analysis. Enzalutamide, abiraterone, ipilimumab, and tasquinimod could improve the median time to chemotherapy, while enzalutamide and bicalutamide could improve the median time to decline of the FACT-P global score (Fig A.5).

In the PFS analysis, 16 trials were included. Of these, 5 investigated the new agents combined with docetaxel, and 11 trials investigated the new agents alone. Figure 1B showed the network of comparisons. A total of 14 trials provided explicit HR and 95% CI. The remaining 2 trials only have the value for the median time to PSA progression, which was used as a substitute. Compared to the placebo, both Bayesian and frequentist random-effects network meta-analyses suggested that enzalutamide (HR=0.21, 95% CI: 0.11–0.38, HR=0.20, 95% CI: 0.15–0.29, respectively) and abiraterone (HR=0.30, 95% CI: 0.13–0.71, HR=0.30, 95% CI: 0.18–0.49, respectively) had significant improvements in PFS (Figure 2B). The results of our analysis were consistent (Fig A.6). The results of the two frame networks were

similar. Also, bicalutamide had significant benefits in PFS in frequentist network, and the other new agents did not present any clinical value. As shown in Figure 2B, the indirect comparison of HR between enzalutamide and abiraterone was 0.57 (95% CI: 0.46–0.70). However, the differences were insignificant in both Bayesian and frequentist network meta-analysis (HR=0.69, 95% CI: 0.24–2.00, HR=0.68, 95% CI: 0.37–1.20, respectively). Furthermore, the P-score of enzalutamide was 0.98, and that of abiraterone was 0.84.

All new agents in combination with docetaxel did not show any significant improvements in PFS in Bayesian network meta-analysis. Only bevacizumab combined with docetaxel showed a significant benefit in PFS in frequentist network meta-analysis (HR=0.80, 95% CI: 0.71–0.91) (Fig A.4B).

In rPFS analysis, 8 trials were included. However, none investigated the new agents combined with docetaxel. Figure 1C showed the network of comparisons. Eight trials provided explicit HR and 95% CI. Compared to the placebo, both network meta-analyses suggested that enzalutamide (HR=0.21, 95% CI: 0.11–0.38, HR=0.20, 95% CI: 0.15–0.29, respectively), abiraterone (HR=0.30, 95% CI: 0.13–0.71, HR=0.30, 95% CI: 0.18–0.49, respectively), and bicalutamide (HR=0.30, 95% CI: 0.13–0.71, HR=0.30, 95% CI: 0.18–0.49, respectively) effectuated significant improvements in rPFS (Data were shown in Figure 4A). Moreover, tasquinimod and orteronel had a positive outcome in rPFS only in frequentist network. Different from the above results, enzalutamide was more advantageous than abiraterone in rPFS in indirect comparison and Bayesian and frequentist network meta-analysis (HR=0.69, 95% CI: 0.24–2.00, HR=0.68, 95% CI: 0.37–1.20, HR=0.68, 95% CI: 0.37–1.20, respectively). The P-score of enzalutamide was 1.00, and the score of abiraterone was 0.67.

As most trials reported that grade ≥3 AEs, a network meta-analysis was performed. As shown in Figure 1D and 4B, compared to the placebo, ipilimumab and tasquinimod led to more AEs in both models. Additionally, abiraterone and orteronel led to more AEs in frequentist network. However, no significant differences were detected between enzalutamide and abiraterone (Figure 4B). We summarized the rankings of eight novel treatments strategies in terms of OS and AEs based on P-values (Figure 5). Enzalutamide and abiraterone had similar benefits/harm and ranked as the best and second-best treatment, respectively, while. Ipilimumab and orteronel were ranked as the worst and second worst in terms of AEs.

Discussion

Novel agents are essential for an improved outcome in CRPC patients. Currently, several new agents have been widely tested in pre-docetaxel setting or in combination with docetaxel. However, only a few trials report the comparison of these novel agents directly. Therefore, treatment patterns for chemotherapy-naïve CRPC patients are challenging. To overcome these limitations, we created a network meta-analysis to compare the efficacy and safety of these novel treatments.

Overall survival is a critical endpoint for patients, which is the primary outcome of our study.[33] In addition, the network meta-analysis in OS and its subgroup analysis is the major finding of this study. The current results showed that only enzalutamide and abiraterone could improve the OS significantly in chemotherapy-naïve CRPC patients as compared to the placebo. These findings were confirmed by Bayesian and frequentist network meta-analysis, and the other novel agents were a failure. Therefore, we proposed that these two novel agents should be used as second-line hormonal therapy after first ADT therapy failure for chemotherapy-naïve CRPC patients.

Nevertheless, whether enzalutamide or abiraterone is optimal is yet to be elucidated. Any trial comparing these two effective agents directly has not yet been reported. The network meta-analysis has overcome these limitations to derive a precise estimation based on the existing conditions. For instance, the HR of OS/PFS/rPFS for enzalutamide reported in the included trials was much lower than that for abiraterone. In addition, the indirect comparison suggested that enzalutamide is advantageous on PFS/rPFS. However, the current network meta-analysis revealed that both agents have almost the same survival benefit on OS and PFS without significant difference. Enzalutamide only improved the rPFS of patients more effectively than abiraterone. This conclusion was supported by P-values in this analysis. In the subgroup analysis, enzalutamide showed a more comprehensive benefit than abiraterone. In any subgroups of patients with age <75, ≥75, or ECOG score=0, 1 or Gleason score ≤7, ≥8, enzalutamide proved to improve the OS significantly. Nevertheless, the significant benefit of abiraterone can only be found in patients with age <75 and ECOG score=0. In addition, the P-score of enzalutamide was always higher than abiraterone in all subgroups reported. With respect to the toxicities, our network did not detect any significant differences between the two agents. In summary, abiraterone is suitable for younger and better general health status patients, while enzalutamide has a wider application area. Based on the P-values, even in the younger and better patients, enzalutamide is optimal treatment.

To the best of our knowledge, this is the first network meta-analysis to compare the efficacy and safety of novel agents in chemotherapy-naïve CRPC patients and provides a precise estimate of HRs for OS/PFS/rPFS. The current study has some advantages. First, we included 23 studies with 13 novel agents that are popular research drugs in CRPC treatment. Second, the current results were strengthened by the methods we used. In our network, we used both Bayesian and frequentist network meta-analyses, to derive a more precise results based on the existing evidence. The network overcomes the difficulties of single meta-analysis and the results were consistent. Interestingly, the network allowed the comparisosn of the two effective agents (enzalutamide and abiraterone) in the absence of direct comparison and derived precise effects by jointly assessing the direct and indirect comparisons. This network provides new insights on treatments in chemotherapy-naïve CRPC patients and references for clinical and future research.

Nevertheless, the current network analysis also had some limitations. First, only a few studies compared these new agents. Most of the trials compared the new agents with placebo. Thus, this network needs to be verified further by direct clinical trials. To date, network meta-analysis is an optimal choice. Second, most trials lack detailed, unified subgroup data, such that a comprehensive subgroup analysis is not

feasible. Moreover, a racial or clinical subgroup analysis could be conducted by future clinical research. Third, our network was based on the summary statistics instead of individual patient data.[16] Although detailed individual data can increase the power of network meta-analysis, it is challenging for researchers to acquire these data.

Conclusion

In summary, this network meta-analysis suggested that both enzalutamide and abiraterone are the best optimal treatment in chemotherapy-naïve CRPC patients with age <75 and ECOG score = 0 for great improvement in OS and PFS. In addition, enzalutamide is also an optimum therapy for chemotherapy-naïve CRPC patients with age ≥75 and ECOG score = 1. Besides, additional studies on other novel agents are still needed in the near future to improve outcomes of CRPC patients despite the current remarkable achievements.

Abbreviations

Chemotherapy-naïve castration-resistant prostate cancer (CRPC)

Prostate cancer (PCa)

American Society of Clinical Oncology (ASCO)

Relative hazard ratios (HR)

Overall survival (OS)

Progression-free survival (PFS)

Radiographic PFS (rPFS)

Adverse events (AEs)

Declarations

Ethics approval and consent to participate: none

Consent for publication: none

Availability of data and materials: none

Competing interests: none

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Authors' contributions: ZhiChao Min: screened database and extracted data, prepared figures, study concept and design, writing and editing.

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Figures

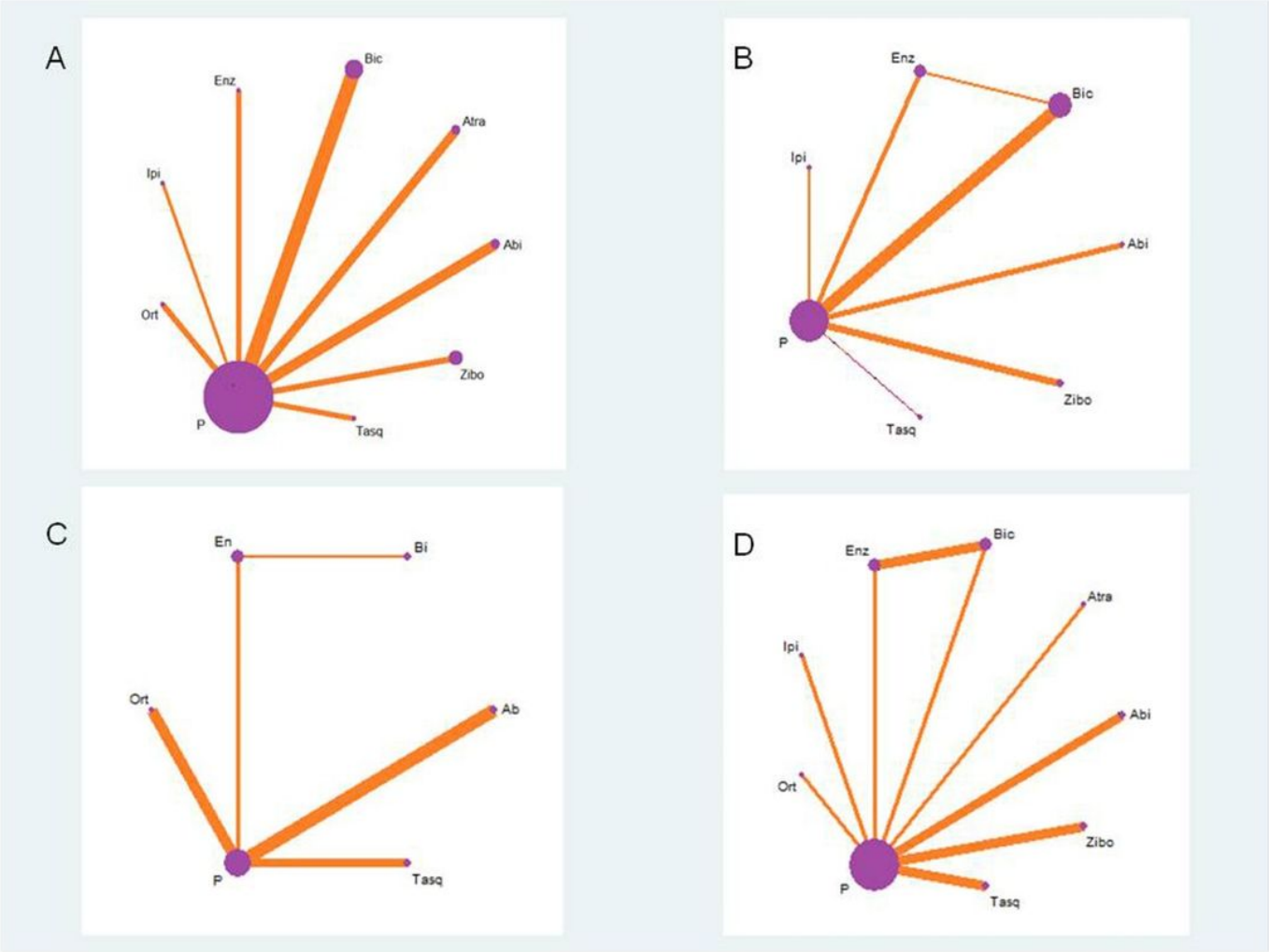

Figure 1

Network of the comparisons in network meta-analysis. (A) in OS analysis. (B) in PFS analysis. (C) in rPFS analysis. (D) in AEs analysis. Each nodes corresponds to the treatment included in the analysis, with the area proportional to the number of patients. Each line represents direct comparisons between treatments, with the width corresponding to the number of trials comparing the treatments directly.

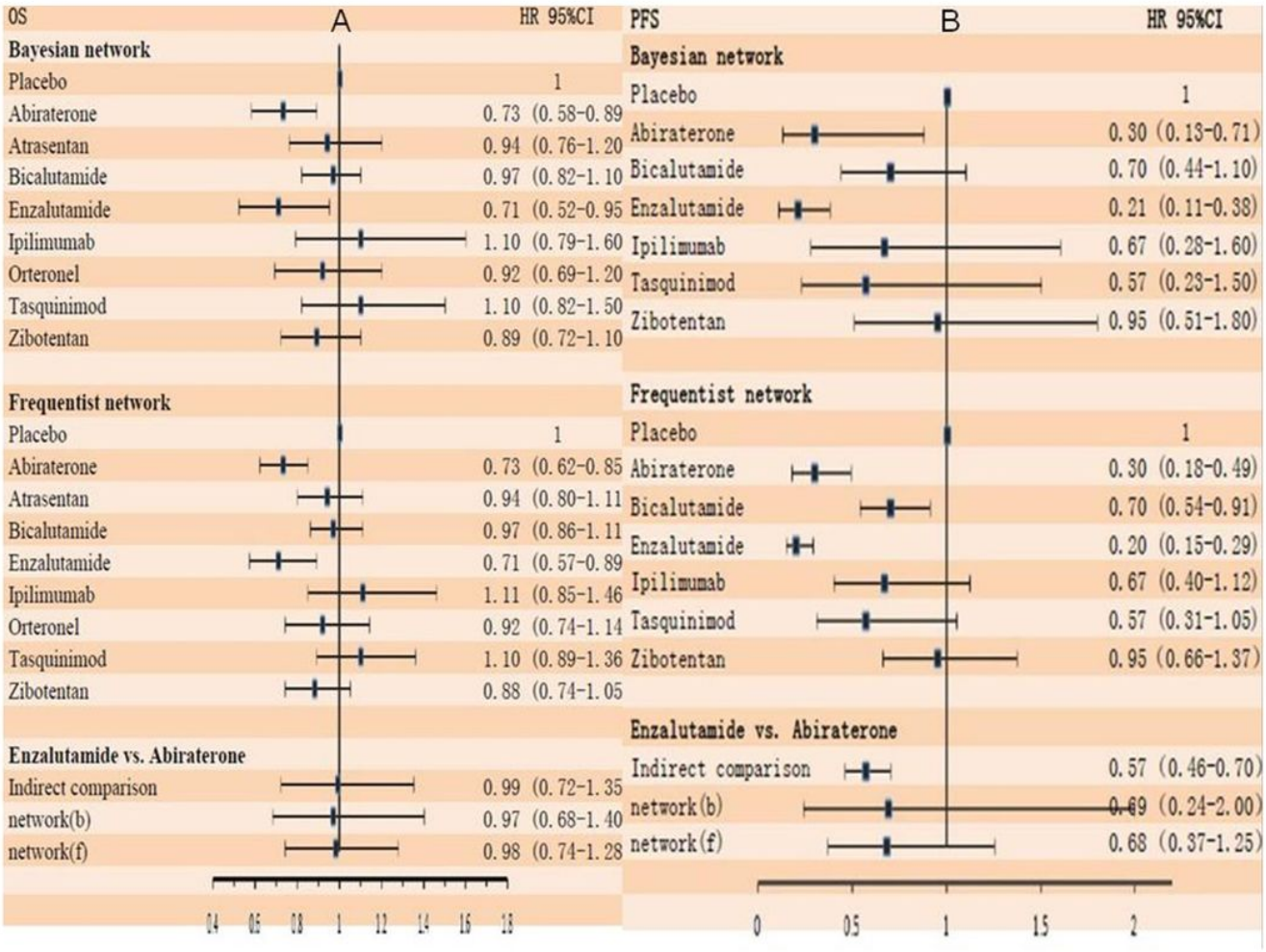

Figure 2

Pooled hazard ratios for OS (A) and PFS (B) by Bayesian and frequentist network meta-analysis compared with placebo. CI=credible interval. HR= hazard ratios. b= Bayesian model. f= frequentist model.

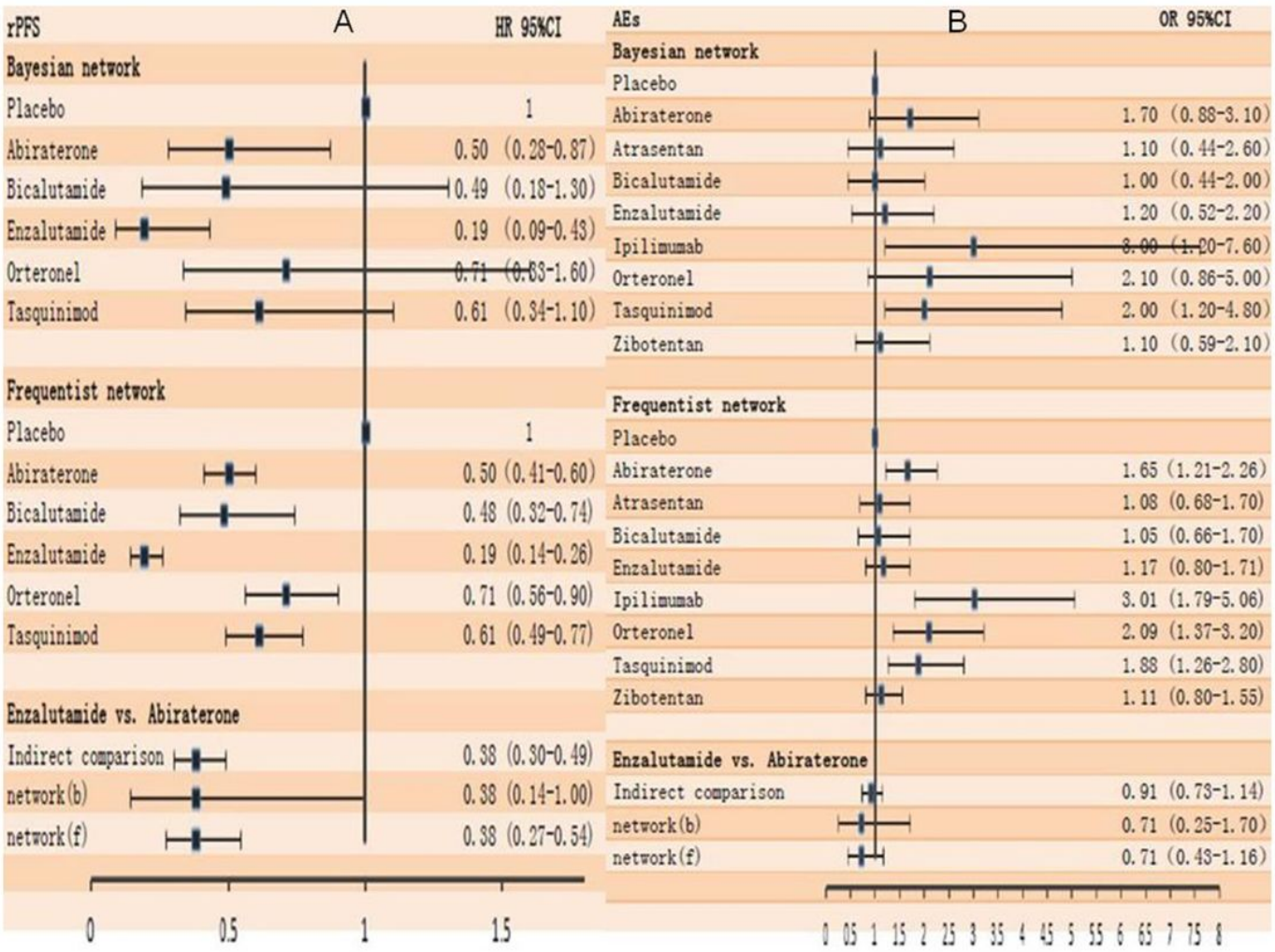

Figure 3

Treatment comparisons in the subgroup of network meta-analysis for OS and P-scores.

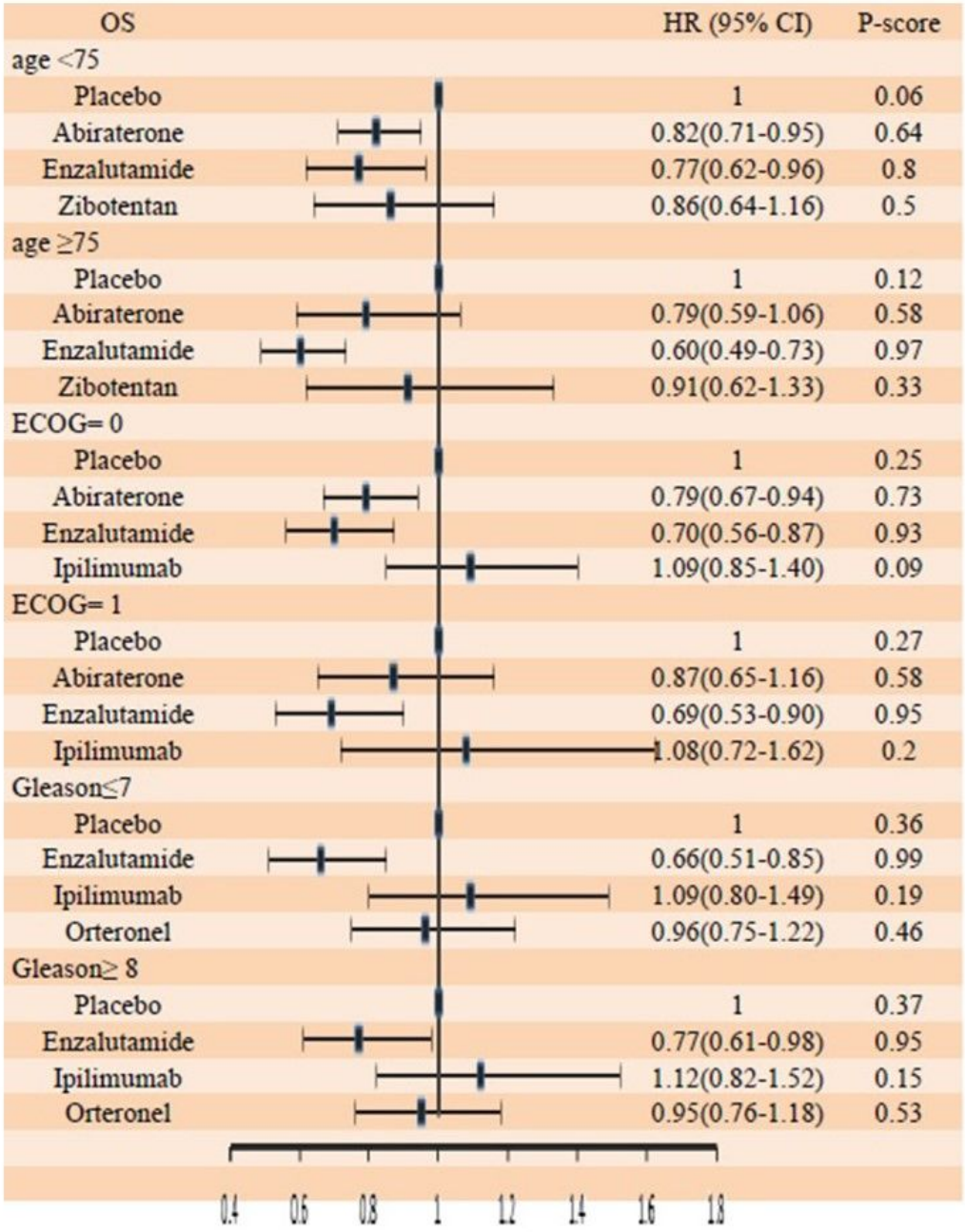

Figure 4

Pooled hazard ratios for rPFS (A) and AEs (B) by Bayesian and frequentist network meta-analysis compared with placebo. CI=credible interval. HR= hazard ratios. b= Bayesian model. f= frequentist model.

	P-score			
	OS	PFS	rPFS	AEs
Abiraterone	0.92	0.84	0.67	0.34
Atrasentan	0.48	NA	NA	0.73
Bicalutamide	0.4	0.44	0.66	0.76
Enzalutamide	0.93	0.98	1	0.65
Ipilimumab	0.16	0.45	NA	0.03
Orteronel	0.53	NA	0.25	0.18
Placebo	0.31	0.08	0	0.84
Tasquinimod	0.15	0.55	0.41	0.25
Zibotentan	0.63	0.15	NA	0.71

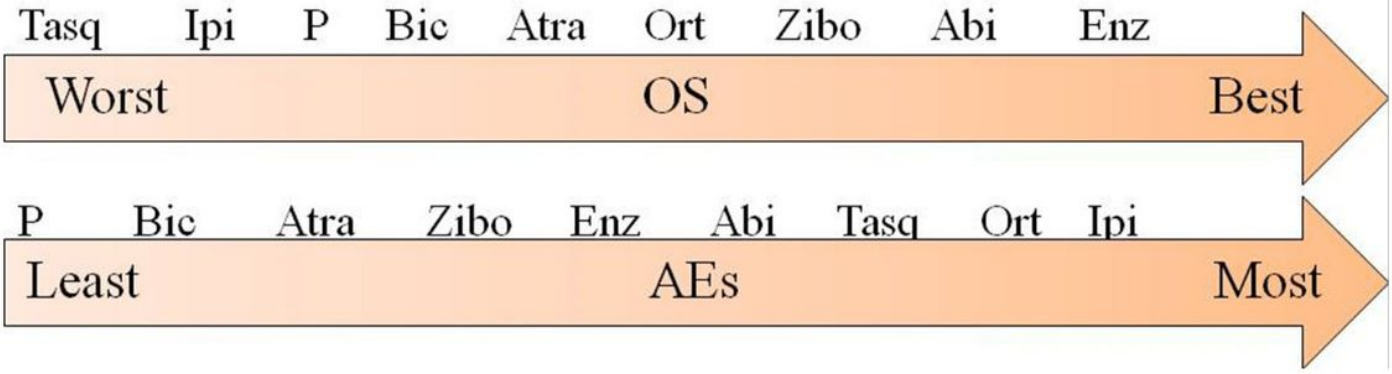

Figure 5

P-scores of treatments in OS, PFS, rPFS and AEs. Ranking of treatments in terms of OS benefit and overall ≥3 AEs based on P-scores. P= placebo, Abi= Abiraterone, Atra= Atrasentan, Bic= Bicalutamide, Enz= Enzalutamide, Ipi= Ipilimumab, Ort= Orteronel, Tasq= Tasquinimod, Zibo= Zibotentan.

Supplementary Files

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