Original Article

# Combination therapy in metastatic castration sensitive prostate cancer: A Systematic review and network meta-analysis

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## ABSTRACT

**Introduction:** Studies directly comparing the different combination therapies offered to men with metastatic castration sensitive prostate cancer (mCSPC), are not available yet. This study was designed using the network meta-analysis (NMA) framework to provide a comparison of the different available options for the treatment of men with mCSPC.

**Methods:** A systematic search was performed and the prospective randomized controlled trials reporting the overall survival (OS) or failure-free survival (FFS) were selected for review. A total of 14 studies were included in the NMA.

**Results:** The addition of abiraterone, apalutamide, docetaxel, and docetaxel with zoledronic acid to the androgen deprivation therapy (ADT) demonstrated a significant improvement in the OS. In indirect comparison, abiraterone had a higher impact on the OS as compared to docetaxel (hazard ratio [HR]: 1.21, 95% confidence interval [CI]: 1.0–1.46) and docetaxel with zoledronic acid (HR: 1.31, 95% CI: 1.05–1.63) but not apalutamide. Furthermore, apalutamide was not different than docetaxel or docetaxel with zoledronic acid. There was a significant improvement in the FFS with the combination of abiraterone, apalutamide, docetaxel (HR: 0.61, 95% CI: 0.46–0.81), docetaxel with zoledronic acid (HR: 0.62, 95% CI: 0.43–0.9), and enzalutamide (HR: 0.39, 95% CI: 0.25–0.61) as compared to the ADT alone. Similar to the indirect comparison of OS, abiraterone outperformed docetaxel (HR: 1.66, 95% CI: 1.12–2.47), docetaxel with zoledronic acid (HR: 1.69, 95% CI: 1.06–2.68), and enzalutamide (HR: 1.06, 95% CI: 0.63–1.80), but not apalutamide in terms of impact on the FFS.

**Conclusion:** Overall, abiraterone demonstrated better OS and FFS outcomes as compared to all the other combination strategies in this NMA.

## INTRODUCTION

Prostate cancer (PCa) is the most commonly diagnosed noncutaneous cancer in men and the second leading cause of death from cancer in the United States.[1] Following the United States Preventive Task Force recommendation against prostate-specific antigen (PSA) screening, the incidence of metastatic PCa (mPCa) has been increasing in the United States.[2-4] There is a substantial risk of mortality in men over 70 years of age diagnosed with PCa with a Gleason score (GS) >7 or a serum PSA >20 ng/mL. Furthermore, the risk for death from mPCa directly correlates with the GS, with the PCa-specific mortality rising from 10% to 30% for GS ≤7

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to >50% for GS >7.[5] Medical or surgical castration is well established treatment and improves the symptoms in men with mPCa; however, the improvement in survival remains controversial. Recently, several combination strategies that include castration have consistently and unequivocally shown improvement in the overall survival (OS) of men with mPCa.[6-21]

Several combinations along with castration have been evaluated in the treatment of men with metastatic castration sensitive PCa (mCSPC) including abiraterone, apalutamide, celecoxib, docetaxel, enzalutamide, first-generation antiandrogens (FAA), radiotherapy, and zoledronic acid. Currently, there is no standard guideline for selecting one of the combination strategy over another in the treatment of men with mCSPC. Recently, a meta-analysis performed to evaluate the impact of radiotherapy in mPCa has demonstrated that radiotherapy at least does not appear to be harmful and may be beneficial in patients with low-metastatic burden and good general condition.[22] Moreover, a direct comparison of efficacy of the different combination strategies is lacking, which makes the treatment selection challenging.

In the recent years, network meta-analysis (NMA) has become a popular tool to provide an indirect comparison of the different treatment options. NMAs comparing a few of the treatment combinations in mCSPC have been reported.[13-17] In a recent NMA, Sathianathen *et al*.[23] did not find a difference in the OS when comparing the various combination options. However, Sathianathen *et al*.[23] did not include the ARCHES (NCT02677896) trial which compared androgen deprivation therapy (ADT) with enzalutamide or a placebo.[14] As with any meta-analysis, the addition of new data can change the results of the analysis. In this study, we performed an updated systematic review of the literature and analyzed the available combination options for mCSPC using the NMA methodology to come up with a rank order of the available treatment options based on the efficacy and the side effect profile of the various available combination strategies.

## METHODS

Medline, Embase, ClinicalTrials.gov, and the Cochrane Central Register of Controlled Trials were searched using database-specific search strategies. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines in our search strategy and data selection. In addition, the reference lists of the review articles and the bibliographies of the identified trial reports were screened for further eligible trials. ClinicalTrial.gov was further searched for ongoing trials.

The search was limited to English language literature only. The primary search was performed in December 2019 and was updated on April 10, 2020. Key search terms included metastatic hormone sensitive (castration sensitive or hormone naïve or castration naïve) PCa, neoplasm, tumor, celecoxib, zoledronic acid, docetaxel, abiraterone acetate plus prednisolone, apalutamide, enzalutamide, and radiotherapy.

### *Eligibility criteria*

Two independent researchers (JK and SBJ) screened the search results and selected the articles. We selected only prospective randomized control trials (RCT) exclusively involving men with mCSPC, comparing ADT to ADT with a combination of another drug (s) or treatment. Articles were included only if OS, failure-free survival (FFS), progression-free survival (PFS), or graded adverse events (AEs) were reported. Trials evaluating patients with metastatic castration resistance PCa (mCRPC) were excluded.

### *Data extraction*

Four authors (JK, SBJ, DN, and SS) independently extracted the data from full text articles. We generated a data extraction template in Microsoft Excel. The hazard ratio (HR), standard error (SE) with confidence interval (CI) and the *P* value for OS, FFS, and AE ≥Grade 3 were extracted, when available. In cases where the HR, CI, or SE was not available, we used the previously described methods to compute the respective values from the reported data.[24] To ensure the appropriateness and consistency among the trials, the outcome definitions were standardized. The inclusion criteria of the trials were reviewed to ensure transitivity of the results. Additional data including the total number of patients, demographic information, recruitment period, treatment schedules, median follow-up, and AEs were extracted into a separate data template document. Assessment of the study quality for all the trials was carried out using the Cochrane risk of bias tool.[25]

### *Analysis*

The analysis of the endpoints was performed using NMA network suite of commands with STATA statistical software (*v 15*. College Station, TX: StataCorp LLC.). Except for the Systemic Therapy in Advancing or Metastatic PCa: Evaluation of Drug Efficacy (STAMPEDE) trial, all the other trials included in the analysis were two-arm comparisons between ADT and ADT in combination with another agent(s). We assessed the global inconsistency to reflect the heterogeneity between STAMPEDE and the other trials.

To demonstrate the relationship between various combinations used, network diagrams were generated as shown in Figure 1. For analysis purposes, we grouped studies that used bicalutamide, flutamide, and nilutamide under FAA. Estimates of the relative effect for each pairwise treatment comparing the primary consistency model were estimated on the HR scale along with a corresponding 95%

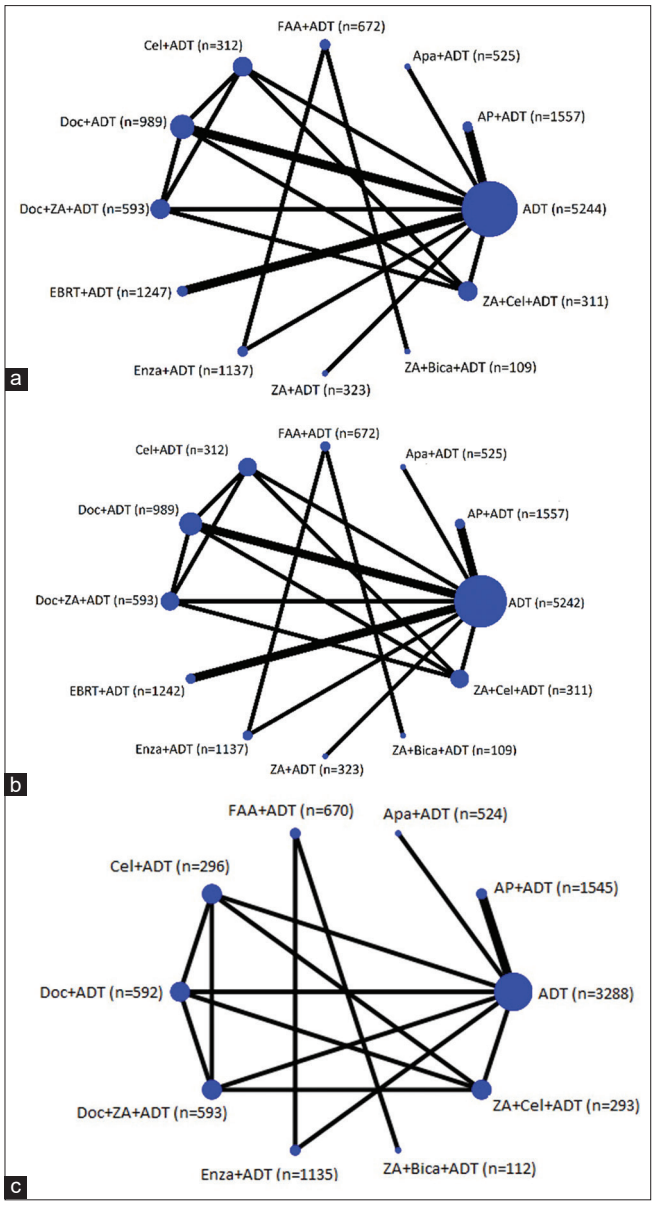


**Figure 1:** Network treatment comparisons for all the studies investigating the treatment options for metastatic castrate sensitive prostate cancer. Figure shows network diagram for (a) overall survival, (b) failure-free survival, and (c) adverse events Grade 3 or more. The node size corresponds to the number of trials in which the treatments were studied and the number of patients is shown adjacent to the node. Interventions that are compared directly are joined with a line, the thickness of which corresponds to the number of trials that assessed the comparisons. Abbreviations of interventions are listed in text

CI and displayed as network forest plots. The network treatment rankings were also calculated and summarized as a surface under the cumulative rank (SUCRA) score.[20] For the pictorial representation of the relative ranks for the treatments analyzed, the rank probability graphs were constructed.

## RESULTS

Overall, the search resulted in 1,702 articles after the removal of the duplicates. A total of 14 trials were identified for the analysis [Supplementaries 1 and 2]. All combinations were added to the ADT. There were two trials for each of the following interventions as compared to the ADT alone. These combinations included abiraterone plus prednisolone (AP + ADT), external beam radiotherapy plus ADT (external beam radiation therapy [EBRT] + ADT), and docetaxel plus ADT (Doc + ADT). The other studies comparing ADT to apalutamide plus ADT (Apa + ADT), enzalutamide plus ADT (Enza + ADT), zoledronic acid plus ADT (ZA + ADT), docetaxel plus zoledronic acid plus ADT (Doc + ZA + ADT), zoledronic acid plus celecoxib plus ADT (ZA + Cel + ADT), and celecoxib plus ADT (Cel + ADT) were assessed in a single trial each. Furthermore, enzalutamide plus ADT (Enza + ADT) and zoledronic acid plus bicalutamide plus ADT (ZA + Bica + ADT) were compared to FAA plus ADT (FAA + ADT).

In total, 18,263 men were included in the NMA with 5,244 men randomized to receive ADT alone and 13,019 men to receive ADT in combination with one of the interventions. OS and FFS were reported in all of the trials. Most of the studies had an intermediate risk of bias and all the studies had low risk of bias in randomization as shown in Supplementary Figure 1.

The definition of FFS included the time to PSA or clinical progression or death for all of the trials except for the LATITUDE (NCT01715285) and the CHAARTED (NCT00309985) trials. In the LATITUDE trial, FFS was defined as the time to radiographic progression or death from any cause, and in the CHAARTED trial, the FFS was the time to PSA rise or clinical progression but not the time to death. For analytic purposes, we have not differentiated between these definitions of FFS.

### *Overall survival*

The results of the OS analysis are shown in Figure 2. The analysis showed that as compared to the ADT, AP + ADT (HR: 0.63, 95% CI: 0.54–0.72), Apa + ADT (HR: 0.67, 95% CI: 0.51–0.89), Doc + ADT (HR: 0.75, 95% CI: 0.66–0.86), and Doc + ZA + ADT (HR: 0.82, 95% CI: 0.69–0.97) demonstrated a significant improvement in the OS. However, no significant improvement in the OS were noted for the combination of FAA + ADT, Cel + ADT, EBRT + ADT, Enza + ADT, ZA + ADT, ZA + Bica + ADT, or ZA + Cel + ADT over ADT alone. The SUCRA values for AP + ADT, Apa + ADT, Doc + ADT, and Doc + ZA + ADT were 0.9, 0.9, 0.7, and 0.6, respectively, as shown in Figure 3. Based on the ranking analysis, AP + ADT and Apa + ADT had 54.0% and 28.2% probability of being the first rank treatment, respectively. On the other hand, FAA + ADT had the highest probability of being the last treatment option (59.8%) [Supplementary Figure 3].

### *Failure-free survival*

There was a significant improvement in the FFS with the combination of ADT + AP (HR: 0.37, 95% CI: 0.28–0.49),

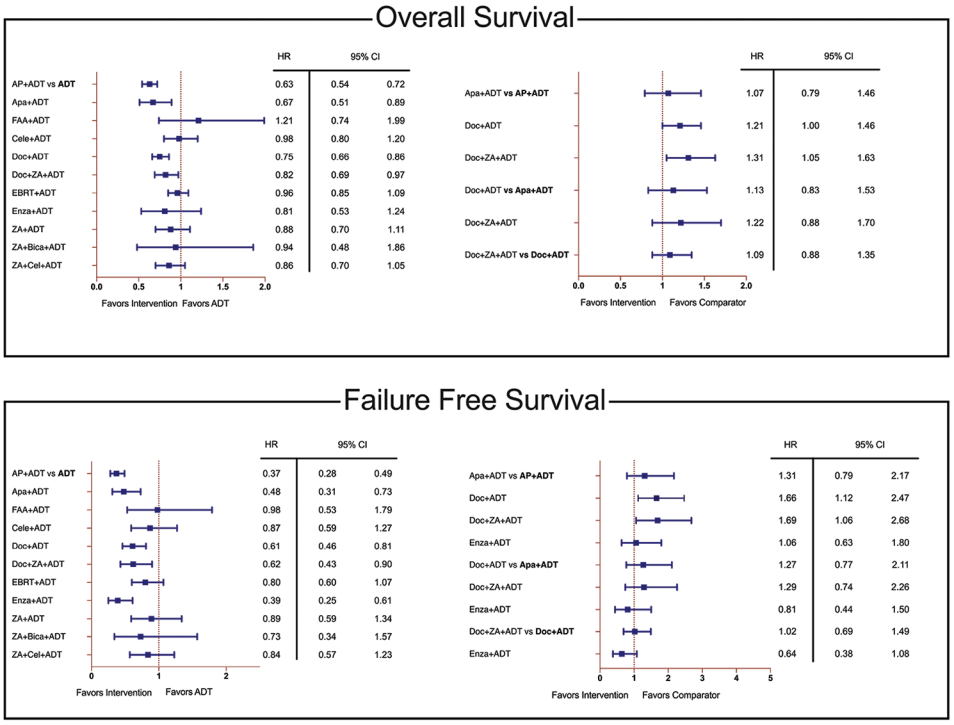


**Figure 2:** Forest plots showing the result of network meta-analysis of the combination strategies used in the treatment of men with metastatic castration sensitive prostate cancer. Treatment abbreviations are defined in the text

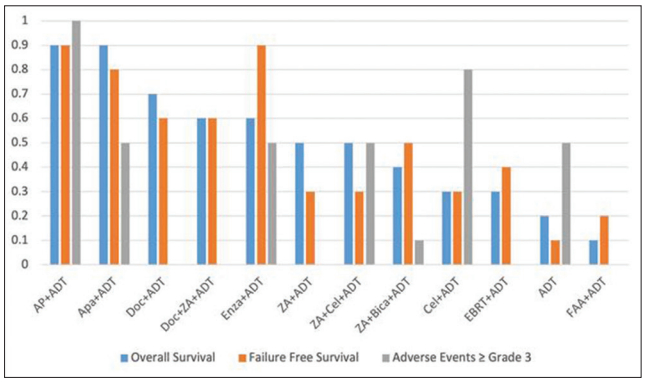


**Figure 3:** Surface under the cumulative rank values for the interventions compared to androgen deprivation therapy in improving the overall survival, failure-free survival, and adverse events ≥Grade 3. Treatment abbreviations are listed in the text

Apa + ADT (HR: 0.48, 95% CI: 0.31–0.73), Doc + ADT (HR: 0.61, 95% CI: 0.46–0.81), Doc + ZA + ADT (HR: 0.62, 95% CI 0.43–0.9), and Enza + ADT (HR: 0.39, 95% CI: 0.25–0.61) as compared to the ADT alone. However, a statistically significant difference was not seen in the FFS with the combination of FAA + ADT, Cel + ADT, EBRT + ADT, ZA + ADT, ZA + Bica + ADT, or ZA + Cel + ADT as compared to the ADT alone. The SUCRA values for AP + ADT, Enza + ADT, Apa + ADT, Doc + ADT, and Doc + ZA were 0.9, 0.9, 0.8, 0.6, and 0.6, respectively, as shown in Figure 3. Based on the ranking analysis, AP + ADT had the highest probability (51.4%) of being the first rank treatment in the terms of FFS, while Enza + ADT had a 38.2% probability for being the first rank treatment option. FAA + ADT had the highest probability of being the last treatment option (33.7%) [Supplementary Figure 3].

### *Adverse events ≥grade 3*

The combinations of AP + ADT (HR: 0.55, 95% CI: 0.48–0.64), Doc + ADT (HR: 0.58, 95% CI: 0.46–0.73), and Doc + ZA + ADT (HR: 0.66, 95% CI: 0.53–0.84) had more AEs ≥Grade 3 as compared to the ADT alone. However, FAA + ADT had a significantly lower rate of AEs ≥Grade 3 (HR: 1.87, 95% CI: 1.31–2.67) as compared to the ADT alone. Based on the ranking analysis, when combined with ADT, FAA had the highest probability (86.1%) of having the lowest AE ≥Grade 3 [Supplementary Figure 3].

### *Indirect comparison of treatment options*

We performed an indirect comparison of the combinations that had better outcomes compared to the ADT. An indirect analysis for the OS of these treatment combinations was performed in a pairwise manner. The effect of AP + ADT on the OS rate was higher as compared to Doc + ADT and Doc + ZA + ADT, HR: 1.21, 95% CI: 1.0–1.46 and HR: 1.31, 95% CI: 1.05–1.63, respectively. There was no significant difference between the Apa + ADT as compared to Doc + ADT and Doc + ZA + ADT. Doc + ZA + ADT and Doc + ADT had similar OS rates as shown in Figure 2.

Similarly, for FFS, AP + ADT had better FFS as compared to Doc + ADT, Doc + ZA + ADT, and Enza + ADT, HR: 1.66, 95% CI: 1.12–2.47, HR: 1.69, 95% CI: 1.06–2.68, and HR: 1.06, 95% CI: 0.63–1.80, respectively. There was no significant difference between Apa + ADT relative to Doc + ADT, Doc + ZA + ADT, and Enza + ADT. There was no difference between Doc + ADT relative to Doc + ZA + ADT and Enza + ADT as shown in Figure 2.

Combination treatments which had better or worse AE profiles on the direct analysis demonstrated no difference on the pairwise comparisons as shown in Figure 2.

## DISCUSSION

We performed a NMA to indirectly compare the common combination therapies used in the treatment of men with mCSPC. The results for the randomized studies have led to the approval of docetaxel, abiraterone, enzalutamide, and apalutamide, in addition to ADT for the management of men with mCSPC. In our analysis, the addition of abiraterone, apalutamide, docetaxel, or docetaxel with zoledronic acid to ADT improved the OS as compared to the ADT alone. Also, we could demonstrate that AP + ADT had both superior OS and FFS rates compared to Doc + ADT and Doc + ZA + ADT. However, the difference was not significant when compared to Apa + ADT. The results of our NMA are in line with a retrospective analysis of 566 men of the STAMPEDE trial comparing Doc + ADT to AP + ADT.[26] At a median follow-up of 4 years, there was no statistically significant difference in the OS (HR: 1.16, 95% CI: 0.82–1.65) of men with mCSPC treated with docetaxel or abiraterone in the STAMPEDE trial. Moreover, AP + ADT demonstrated a favorable FFS (HR: 0.51, 95% CI: 0.39–0.67) as compared to Doc + ADT.[26]

Unlike our results, a recent NMA by Sathianathen *et al*.,[23] comparing the combination treatments with ADT alone in men with mCSPC, demonstrated an improvement in the OS in men who received enzalutamide in combination with ADT. Sathianathen *et al*.[23] used the data reported in the ENZAMET (NCT02446405) trial in their analysis. There are two differences between our methodology and the inclusion criteria as compared to the NMA by Sathianathen *et al*.[23] First, they excluded the patients in the ENZAMET trial that had received prior docetaxel chemotherapy. However, further analysis of the ENZAMET trial has shown that the survival of patients was not affected by prior docetaxel treatment. In our analysis, we included all the men who participated in the trial regardless of the prior docetaxel treatment status. Second, patients in the ENZAMET trial in the control arm received FAA in addition to the ADT. We have separated these patients from those who received ADT alone. In fact, our analysis showed that the impact of enzalutamide on the OS was significant only when compared to ADT + FAA and not to ADT alone. In addition, we included the ARCHES (NCT02677896) trial comparing Enza + ADT and ADT alone in our analysis. In other words, the results of the EZAMET trial highlight the differences between enzalutamide and FAA. Our NMA did not find a benefit in the OS with the combination of enzalutamide and ADT as compared to the ADT alone which is consistent with the results of the ARCHES trial. We believe that a more comprehensive inclusion criteria and a more restricted selection criteria for the control arm in our NMA has resulted in the lack of significant benefit of Enza + ADT as compared to ADT alone.

AEs ≥Grade 3 were higher in the AP + ADT, Doc + ADT, and Doc + ZA + ADT as compared to the ADT alone and the addition of bicalutamide to ADT lowered the incidence of AEs ≥Grade 3. However, the indirect comparison of these three groups that had a higher incidence of AE ≥Grade 3 failed to demonstrate a significant difference. The results of our analysis are in line with retrospective analysis comparing AP + ADT to Doc + ADT in the STAMPEDE trial, which showed that the incidence of AE ≥Grade 3 was similar for docetaxel (50%) and AP (48%). Although there is no difference in the AE ≥Grade 3 between docetaxel and abiraterone, clinicians may consider the impact of duration of treatment along with the side effect profile in men with mCSPC. Docetaxel is only given for six cycles, but abiraterone may be administered for more than 2 years or until the disease progresses. The type of AE ≥Grade 3 between the two drugs is also different, which may direct the selection of one drug over the other. The cardiovascular AE and febrile neutropenia were more common with abiraterone (9% vs. 3%) and docetaxel (13% vs. 1%), respectively.[27]

Another reason often cited to favour docetaxel is the volume of the disease. Two landmark treatment studies in men with mCSPC, the STAMPEDE, and the CHAARTED demonstrated that docetaxel was the most effective therapy in prolonging the OS in men with high volume metastatic disease, defined as either four or more bone metastases including one or more outside the vertebral body or pelvis, or any visceral metastases, or both. However, we did not perform a subgroup analysis based on the volume of the metastatic disease. The imaging findings in the STAMPEDE and CHAARTED trial were based on the whole-body scintigraphy, computed tomography (CT), or magnetic resonance imaging (MRI); however, MRI is more sensitive than CT and whole-body scintigraphy scan for the detection of mPCa, which may lead to the Will Rogers phenomenon by shifting the patient presumed to have a low volume disease to the high volume disease group.[28] In STAMPEDE trial, docetaxel improved OS in all men with mPCa regardless of the volume of the metastatic disease. The OS improvement was significant in men with high-volume as well as low-volume metastatic disease.[9] Therefore, utilizing the volume status of the disease, while

considering docetaxel therapy in men with mCSPC, may not be a reliable criteria.

Apart from the effect of various combination treatments for castrate sensitive PCa, a recent NMA was also performed to evaluate the effect of different combination treatments for nonmetastatic castrate resistant PCa, which demonstrated that enzalutamide and apalutamide had similar and higher metastasis-free survival rate as compared to darolutamide. In this analysis, darolutamide had better AE profile than the others.[29] Various molecular level researches are underway to improve the understanding of mPCa. In a recently published study, Miyoshi *et al*. demonstrated that median time to castrate resistance was significantly shorter in men with high levels of low-molecular-weight protein tyrosine phosphatase (LMW-PTP) (14.8 months) than those in the low LMW-PTP group (86.3 months, $P < 0.01$). They also demonstrated that age ≥70 years and high LMW-PTP expression were significant predictors of time to castrate resistance.[30] Another study by Liu *et al*. demonstrated that serum neuroendocrine markers could be an effective predictor of treatment outcomes in patients with metastatic castrate resistant PCa.[31]

There are ongoing clinical trials evaluating the combinations of abiraterone and enzalutamide (STAMPEDE, NCT002668476), ADT with docetaxel and darolutamide (ARASENS, NCT02799602), and ADT with TAK-700 (SWOG1216, NCT01809691). Moreover, there are several clinical trials exploring the role of local therapy in men with mCSPC including surgery in SWOG (NCT03678025), g-RAMPP (NCT02454543), TRoMbone (ISRCTN15704862), and radiotherapy in PEACE-I (NCT01957436). Furthermore, the effect of metastasis-directed therapy for oligometastatic disease, including stereotactic radiation in ORIOLE (NCT02680587) and PLATON (NCT03784755), and PSMA radioisotope in STOMP (NCT01558427), is being explored as well. The results of these trials will guide us in selecting the appropriate treatment for men with mCSPC in the future.

We have performed an up-to-date search of the newly published articles; however, treatment of men with mCSPC is evolving rapidly. We have also included the recently published results of the ARCHES trial. However, we readily acknowledge the limitations of the study and caution while translating these findings to the clinical settings. The study relies on the published rather than original data for the analysis. We did not have access to the patient-level data to perform an internal analysis and calculate the original HRs. Caution may also be wise while interpreting the endpoints as the definition of FFS was different for the LATITUDE trial, which included biochemical failure, clinical and radiological progression, whereas other studies used only biochemical recurrence for FFS. The analyzed studies span over almost two decades since 2000, which has also seen dramatic improvements and a glut of newer treatment options are available for men with mPCa. These changes may have resulted in undetectable and unforeseen bias in our analysis.

While it is reasonable to conduct indirect comparisons using NMA framework when direct head-to-head comparative studies are unavailable, the results of indirect comparison using measures of effect magnitude should be viewed cautiously. Many variables including the quality of study, nature of the population studied, the setting of the intervention, and the nature of the outcome measures can affect the apparent treatment efficacies. Although we have carefully selected the evidence from high-quality RCT, the results should be interpreted in the context of limitations of NMA methodology.

## CONCLUSION

In men with mCSPC, the addition of abiraterone, apalutamide, docetaxel, and docetaxel with zoledronic acid to ADT improves the OS. Addition of enzalutamide to ADT did not improve the OS as compared to the ADT alone. The magnitude of improvement in OS in patients receiving abiraterone was higher as compared to patients who recieved docetaxel with zoledronic acid. There was no difference among the other treatment options in improving the OS. Abiraterone, apalutamide, docetaxel, docetaxel with zoledronic acid, and enzalutamide improved FFS when compared to ADT alone. The impact of abiraterone was superior as compared to docetaxel and docetaxel with zoledronic acid in improving the FFS in men with mCSPC.

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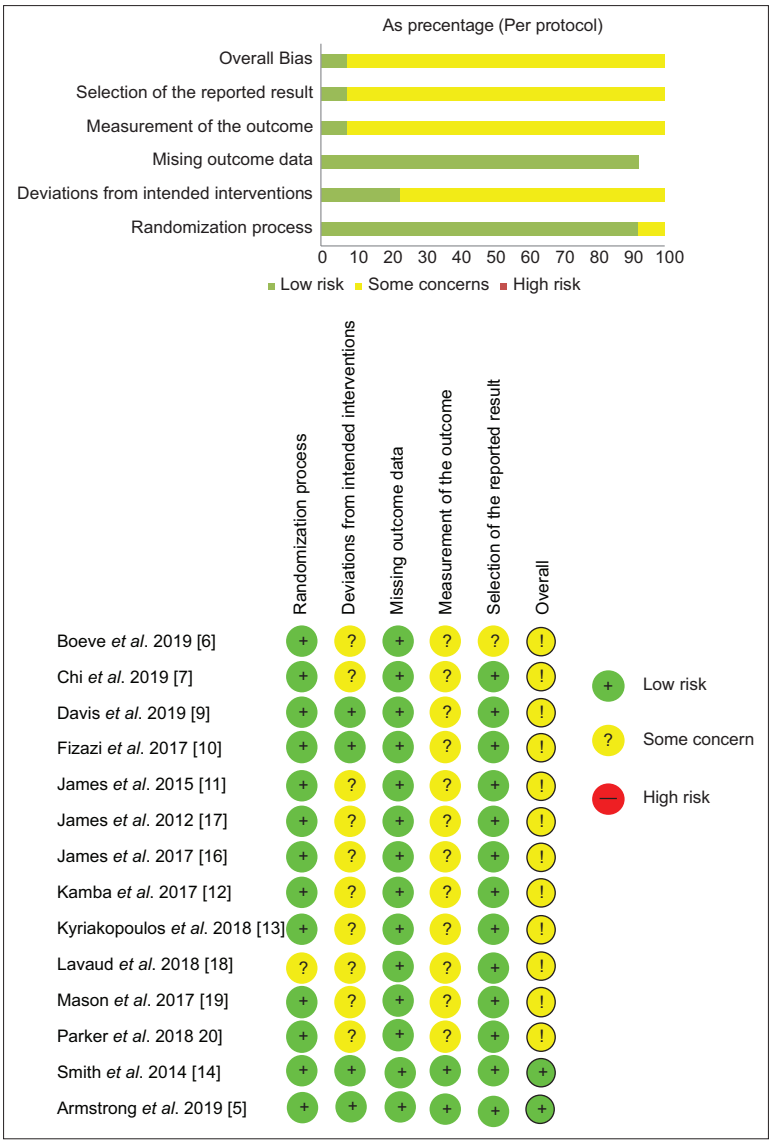
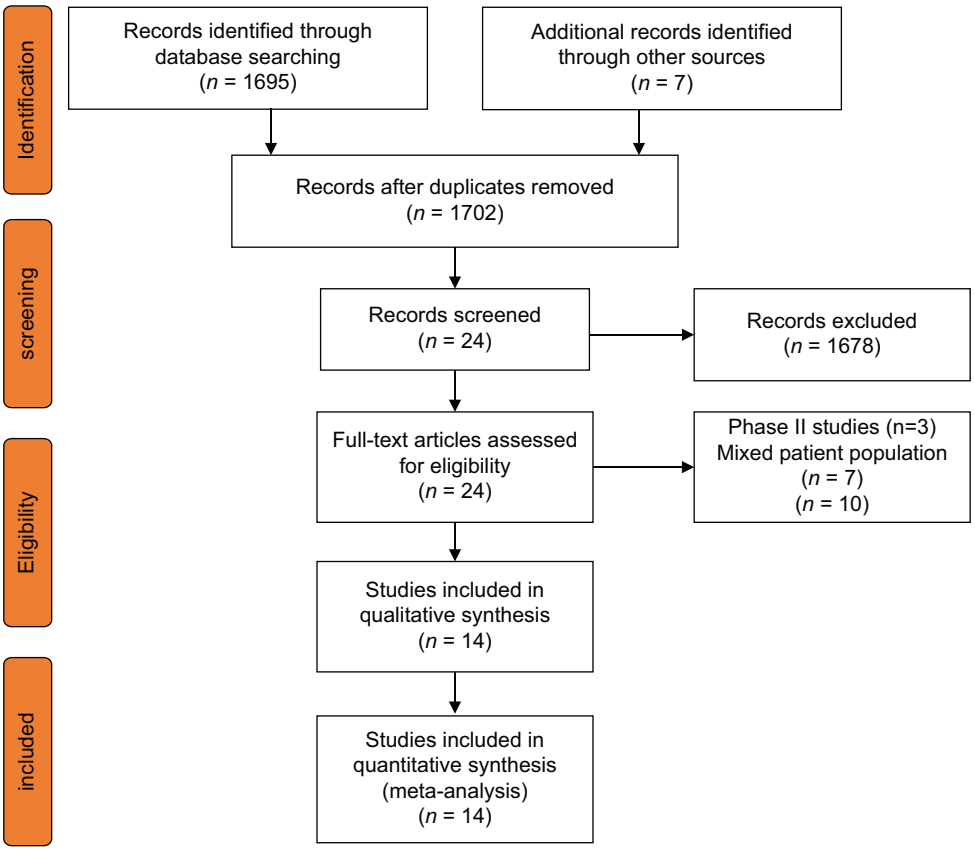
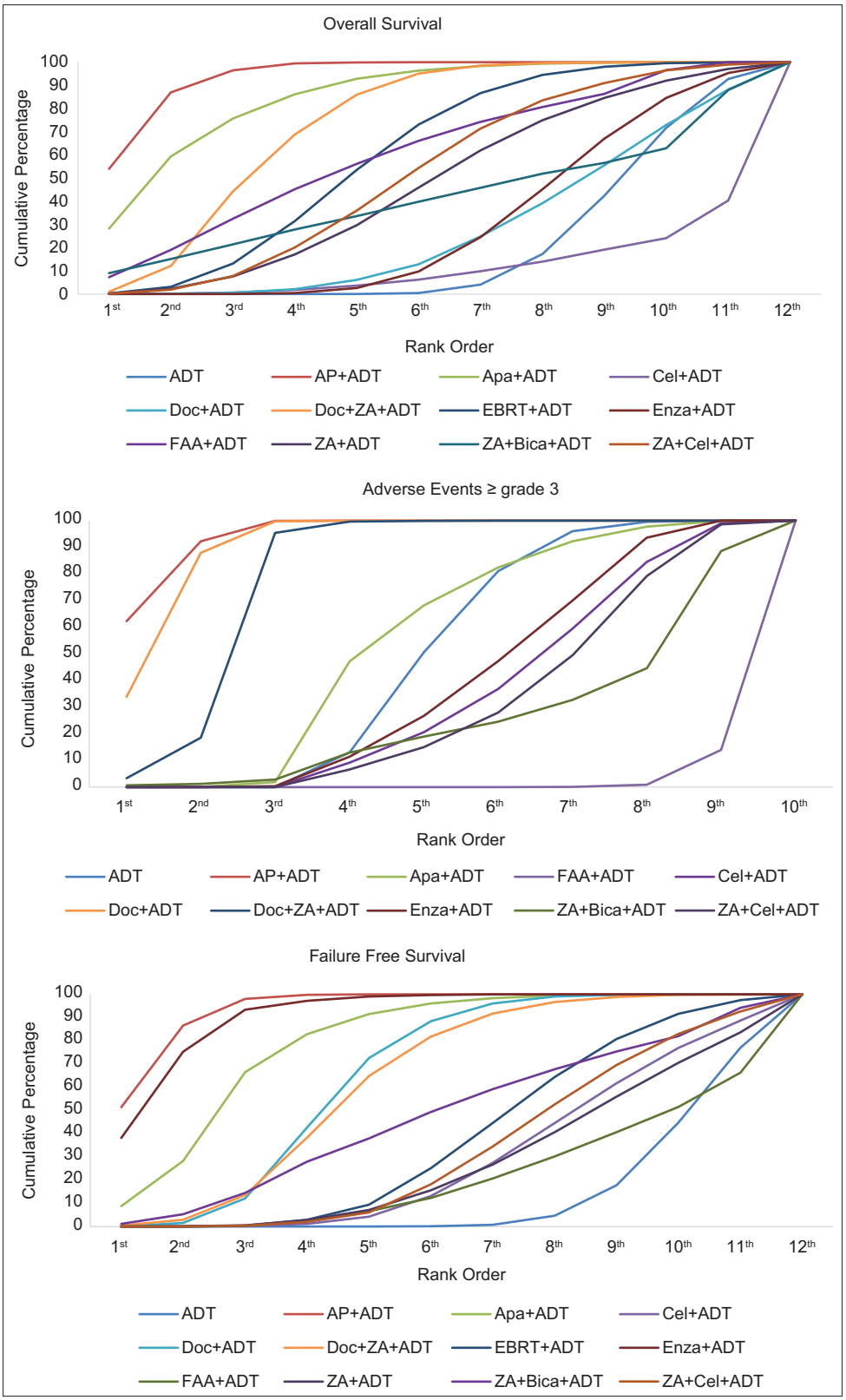



**Supplementary Figure 1:** Risk of bias assessment of the trials used in the network meta-analysis




**Supplementary Figure 2:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses Search Flow Chart




**Supplementary Figure 3:** Cumulative rank order of the interventions in improving overall survival, failure free survival, and adverse events ≥grade 3. Treatment abbreviations are listed in the text