Original article

Treatment of non-metastatic castration-resistant prostate cancer: A systematic review and network meta-analysis

Tratamiento del cáncer de próstata no metastásico resistente a la castración: una revisión sistemática y un metaanálisis

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Abstract

Background: Patients with non-metastatic prostate cancer treated with androgen deprivation therapy develop castration resistance after an average of 19 months. Non-metastatic castration-resistant prostate cancer (M0CRPC) refers to biochemical progression despite medical or surgical castration.

Purpose: To determine the effectiveness of the available interventions for treating non-metastatic castration-resistant prostate cancer (M0CRPC).

Methods: We performed a search strategy in MEDLINE via Ovid, EMBASE, CENTRAL, and LILACS. We included phase II and phase III clinical trials whose primary objective was to evaluate the effectiveness of the intervention in a patient with M0CRPC (primary outcome metastasis-free survival). We excluded studies that included patients with multimodal treatment. We performed the statistical analysis in R and Review Manager 5.3 (RevMan 5.3).

Results: We found a total of 1376 studies. After screening, we selected three studies for qualitative analysis. In the analysis of the three included studies, a total of 4117 patients older than 18 years had non-metastatic castration-resistant prostate cancer. The interventions evaluated were apalutamide, enzalutamide, and darolutamide. All trials demonstrated a significant increase in MFS with the evaluated intervention in patients with nmCRPC. The indirect comparison showed that the three option is better than placebo, but apalutamide and enzalutamide are better than darolutamide.

Conclusion: In non-metastatic patients, CRPC apalutamide and enzalutamide provide a lower risk of metastasis than darolutamide. Also, there were no differences between apalutamide and enzalutamide.

Keywords: Apalutamide, darolutamide, enzalutamide, metastasis-free survival, prostate cancer, nonmetastatic

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Resumen

Antecedentes: Los pacientes con cáncer de próstata no metastásico tratados con terapia de privación de andrógenos desarrollan resistencia a la castración después de un promedio de 19 meses. El cáncer de próstata no metastásico resistente a la castración (M0CRPC) se refiere a la progresión bioquímica a pesar de la castración médica o quirúrgica.
Propósito: Determinar la efectividad de las intervenciones disponibles para el tratamiento del cáncer de próstata no metastásico resistente a la castración (M0CRPC).
Métodos: Realizamos una estrategia de búsqueda en MEDLINE vía Ovid, EMBASE, CENTRAL y LILACS. Se incluyeron ensayos clínicos de fase II y fase III cuyo objetivo principal fue la evaluación de la efectividad de la intervención en un paciente con M0CRPC (resultado primario de supervivencia libre de metástasis). Se excluyeron los estudios que incluyeron pacientes con tratamiento multimodal. Realizamos el análisis estadístico en R y Review Manager 5.3 (RevMan 5.3).
Resultados: Se encontraron un total de 1376 estudios. Después de la selección, se escogieron tres estudios para el análisis cualitativo. En el análisis de los tres estudios incluidos se incluyó un total de 4117 pacientes mayores de 18 años con cáncer de próstata no metastásico resistente a la castración. Las intervenciones evaluadas fueron apalutamida, enzalutamida y darolutamida. Todos los ensayos demostraron un aumento significativo en la SMF con la intervención evaluada en pacientes con nmCRPC. La comparación indirecta demostró que las tres opciones son mejores que el placebo, pero la apalutamida y la enzalutamida son mejores que la darolutamida.
Conclusión: Encontramos que en pacientes no metastásicos CRPC apalutamida y enzalutamida proporcionan un menor riesgo de metástasis en comparación con darolutamida. Además, no hubo diferencias entre apalutamida y enzalutamida.

Palabras clave: Apalutamida, darolutamida, enzalutamida, supervivencia libre de metástasis, cáncer de próstata, no metastásico

Introduction

Prostate cancer is one of the most common cancers in men and is the third leading cause of cancer death in males in the United States. Despite early treatment, around 30 % of patients will relapse.[1]

Since Huggins and Hodges demonstrated the dependence of prostate cancer on androgen signaling, androgen deprivation therapy (ADT) has been the standard of care for metastatic and locally advanced disease.[2] Typically, patients with non-metastatic prostate cancer treated with ADT develop castration resistance after an average of 19 months.[3]

Non-metastatic castration-resistant prostate cancer (M0CRPC) refers to biochemical progression despite medical or surgical castration. In the United States, the incidence of M0CRPC is around 50 000 – 60 000 men per year. It is a relatively indolent disease. However, in the absence of treatment, nearly 33 % of patients will develop bone metastasis at two years.[4]

The Prostate Cancer Working Group (PCWG) 3 defines M0CRPC as a minimum PSA level of 1.0 ng/mL, a rising PSA that is at least two ng/mL higher than the nadir PSA with this rise being at least 25 % over the nadir PSA, castrate levels of testosterone (< 50 ng/mL), and no radiographic evidence of metastases.[5] Once the disease becomes metastatic, overall survival decreases dramatically.[4]

Accordingly, three therapeutic options are currently available for this group of patients in M0CRPC. FDA approved the use of second-generation antiandrogens (enzalutamide, apalutamide, and darolutamide) in 2018. There was evidence for improving metastasis-free survival.[6,7] Nevertheless, there is no available data that supports what the best intervention is. A meta-analysis is an analytical method that provides an estimated bias to a procedure implemented in the clinical context; performing a meta-analysis helps to make better decisions.[8]

This study aimed to determine the effectiveness of the available interventions for the treatment of M0CRPC in terms of metastasis-free survival (MFS).

Methods

We performed a systematic review and meta-analysis according to the recommendations of the Cochrane Collaboration and the PRISMA guidelines. We registered the protocol in PROSPERO CRD42019146966. The search was carried out between April and June 2020.

Inclusion criteria

We included all clinical trials that evaluated intervention in patients with M0CRPC. The inclusion criteria were as follows: phase II and III clinical trials included patients with a diagnosis of M0CRPC, no language restriction. We excluded studies with patients with multi-modal treatment. The primary outcome was the evaluation of metastasis-free survival, which is defined as the time from randomization to confirmed evidence of distant metastasis on imaging or death from any cause, whichever occurred first.

Sources and search strategy.

We performed the search in MEDLINE via Ovid, EMBASE (Scopus), The Central Register of Controlled Trials (CENTRAL), and LILACS from its inception until now (Appendix 1). We also looked for Grey literature (unpublished) in the form of conference abstracts and reference lists of the selected articles. Additionally, we reviewed Google Scholar, thesis databases, and the Open Grey database. We cross-checked the results of these searches to eliminate duplicates. There was no language restriction.

Data collection

We reviewed each reference by title and abstract. Then, we scanned the full texts of relevant studies, applied pre-specified inclusion

and exclusion criteria, and extracted the data. Disagreements were resolved by consensus.

We collected relevant data in duplicate using a standardized data extraction sheet. It contained the following information: author names, year of publication, title, study design, geographic location, objectives, inclusion and exclusion criteria, number of patients included, losses to follow up, timing, the definition of outcomes, outcomes and association measures, and funding source.

Risk of bias

We assessed the risk of bias for each study using the Cochrane Collaboration tool, which covers sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases. We judged the possible risk of bias from extracted information, rated as "high risk," "low risk," or "unclear risk." We computed the graphic representation of potential bias using RevMan 5.3.

Data analysis / Synthesis of results

We performed the statistical analysis in R with the command gem for a Bayesian network meta-analysis and Review Manager v5.3. For outcomes, we reported information about risk differences (RD) with 95% confidence intervals according to the type of variables, and we pooled the data with a fixed effect network meta-analysis according to the heterogeneity expected. We reported the results in forest plots of the estimated effects of the included studies with a 95% confidence interval (95% CI). We evaluated heterogeneity using the I^2 test. For the interpretation, the values of 25%, 50%, and 75% in the I^2 test corresponded to low, medium, and high levels of heterogeneity, respectively.

The transitivity assumption was plausible and evaluated according to the kind of comparisons and considering the similarity of the distribution of the potential effect modifiers across the different pairwise comparisons. Additionally, for every treatment, we estimated the probability of being at each possible rank to infer the relative ranking of the treatments.

Publication bias

We did not perform publication bias because of the lack of studies

Sensitivity analysis

We performed sensitivity analysis, extracting weighted studies and running the estimated effect to find differences.

The geometry of the network

We produced network diagrams to show the evidence available for each outcome and the most frequent comparison. The size of the nodes was proportional to the total number of patients allocated to the treatments across all trials, and the width of the lines was proportional to the total number of RCTs evaluating the comparisons.

Assessment of inconsistency

We evaluated consistency using the node-splitting model through a Bayesian network meta-analysis.

Subgroup analysis

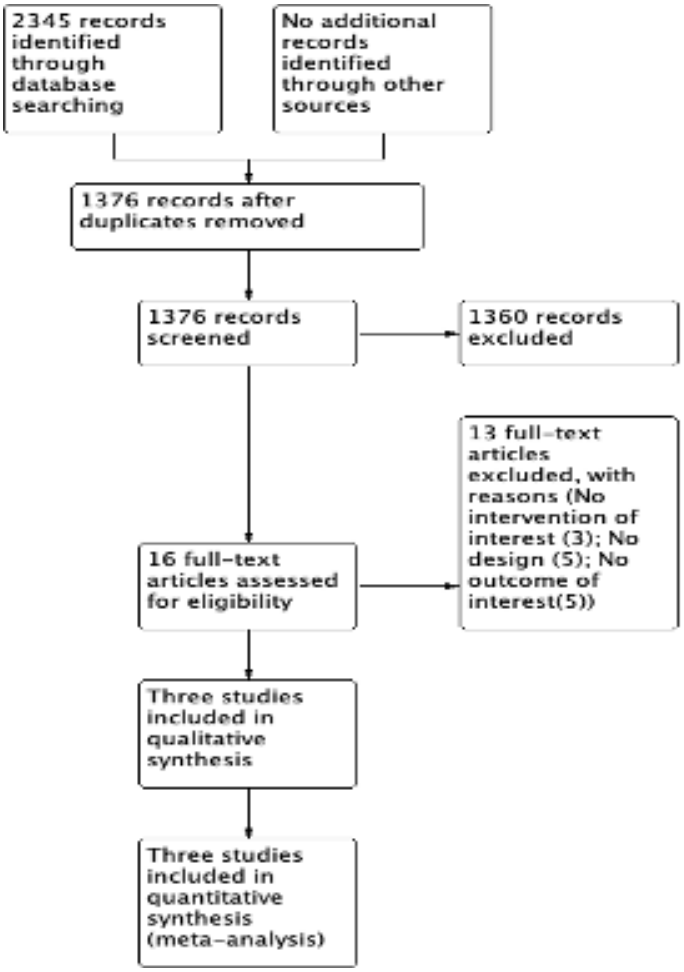
We did not perform any subgroup analysis.

Results

Study selection

We found 2345 studies and 996 duplicates. After the title and abstract review, three studies met the study criteria for full-text analysis (Figure 1).[8–10] All three included studies are randomized clinical trials.

Figure 1 Flowchart of selected studies



Characteristics of included studies

We included randomized clinical trials, blinded, and placebo-controlled. We summarized the characteristics of the studies in Table 1.

Table 1. Characteristics of studies included

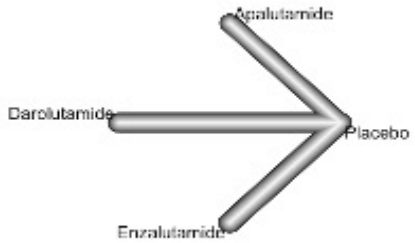
	PROSPER	SPARTAN	ARAMIS
Intervention.	Enzalutamide 160 mg QD vs placebo	Apalutamide 240 mg QD vs placebo	Darolutamide 600 mg BID vs placebo
Design.	Randomized, double-blind, placebo-controlled clinical trial. Phase III	Randomized, double-blind, placebo-controlled clinical trial. Phase III	Randomized, double-blind, placebo-controlled clinical trial. Phase III
Number of patients	1401	1207	1509
Metastatic	M0	M0	M0
Disease	Castration-Resistant	Castration-Resistant	Castration-Resistant
Average (median)	74 years	74 years	74 years
Previous or concomitant therapies	ADT - GnRH – bilateral orchiectomy	ADT - GnRH – bilateral orchiectomy	ADT - GnRH – bilateral orchiectomy
ECOG	0-1	0-1	0-1
Stratified Randomization	PSA Doubling time<six months vs. ≥ six months. Osteoclast-targeted therapy, yes or not.	PSA Doubling time<six months vs. ≥ six months.	PSA Doubling time<six months vs. ≥ six months. Osteoclast-targeted therapy, yes or not.
Symptoms	Asymptomatic	Asymptomatic	Asymptomatic
Follow	25 - 30 months	20.3 months	17.9 months
Gleason	<7 vs > 7	<7 vs > 7	<7 vs > 7
Outcome	MFS 36.6 months vs 14.7 months. HR 0.29; 95 % CI, 0,24 - 0,35; P <0,001.	MFS 40,5 months vs 16.2 months. HR 0·45, 95 % CI 0·32–0·63, P <0,001.	MFS 40.4 months versus 18.4 months HR 0.41 CI 0.34 -0.50 P=<0.001

We included a total of 4117 cases. Among these, 2694 cases were in the experimental group and 1423 cases in the control group 2.[8,9,11]

Summary of Network Geometry

A total of 4117 patients with non-metastatic castration-resistant prostate cancer were included. The primary outcome in the three included studies was metastasis-free survival (MFS). Antiandrogens used in the included studies were: apalutamide, enzalutamide, and darolutamide. The comparison was placebo plus ADT in the three included studies. A total of 1423 patients received the control treatment (Figure 2).

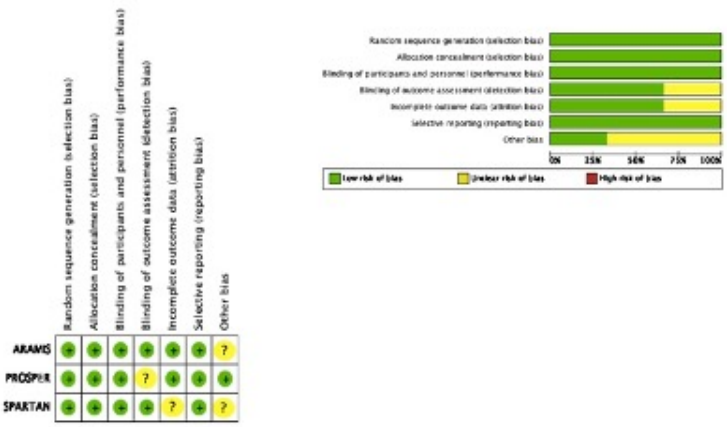
Figure 2 Network geometry



Risk of bias assessment

All the studies were at low risk considering the adequate random sequence generation. Likewise, all reported having made allocation concealment with which the selection bias was low. Additionally, the studies had a low risk of performance bias, given the manifest blinding of participants and personnel. Two of the studies reported on outcome blinding; one study did not report this item, but the risk of detection bias was rated low. The risk of attrition bias and the reporting bias was rated low as well. We summarized the assessment of the risk of bias within and across studies in Figure 3.

Figure 3. Assessment of risk of bias A within studies and B across studies



Exploration for Inconsistency and Ranking

For the MFS outcome, we found no heterogeneity and no inconsistency within and between designs. The rank value (p score) was for darolutamide (0,66), enzalutamide (0,20) and apalutamide (0,13) respectively.

Synthesis of results

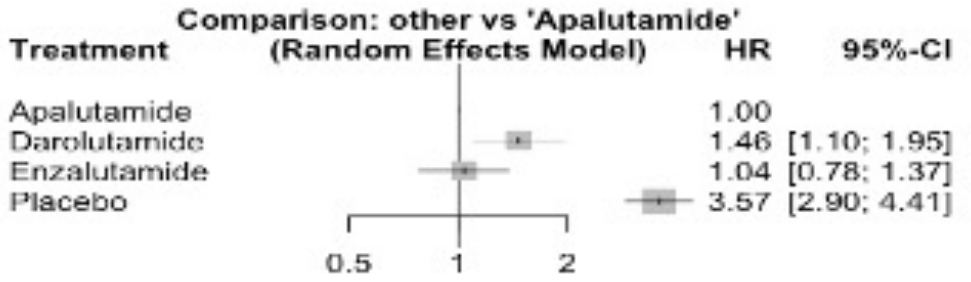
Primary outcome: metastasis-free survival

In total, we included three studies for analysis; The therapies compared were four: apalutamide, enzalutamide, darolutamide, and placebo.

Other interventions versus apalutamide

When comparing darolutamide versus apalutamide, we found an HR 1.46 95 % CI (1.10 to 1.94), favoring apalutamide. There were no significant differences when comparing against enzalutamide (Figure 4a).

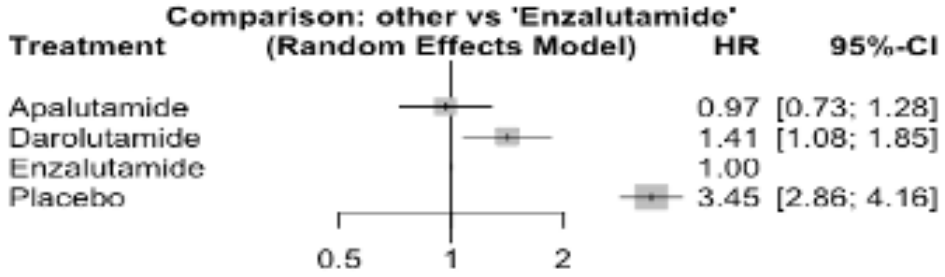
Figure 4a. Forest plot comparison other intervention versus apalutamide



Other interventions versus enzalutamide

We found an HR 1.41 95 %CI (1.08 to 1.85) when comparing darolutamide vs. enzalutamide, favoring the last molecule. We did not find any statistical difference when compared apalutamide vs. enzalutamide (Figure 4b).

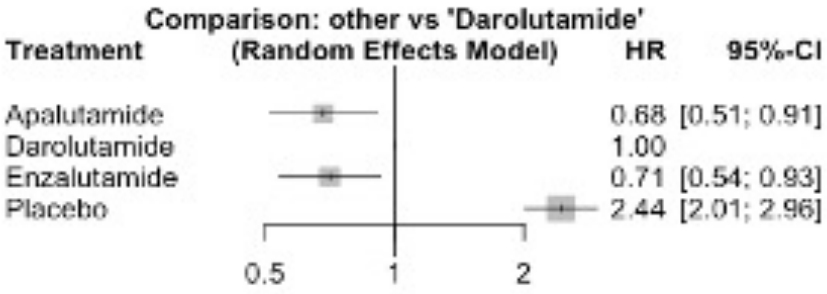
Figure 4b. Forest plot comparison other intervention versus enzalutamide



Other interventions versus darolutamide

We found an HR 0.68 95 % CI (0.51 to 0.90) when comparing apalutamide vs. darolutamide, favoring apalutamide. Similar results favouring enzalutamide (HR 0.71 95 % CI (0.54 to 0.93) (Figure 4c).

Figure 4c. Forest plot comparison Other intervention versus darolutamide



Discussion

Summary

We found a lower risk of metastasis with apalutamide and enzalutamide when compared to darolutamide. Also, there were no statistical differences in the comparison of apalutamide vs. enzalutamide.

Contrast with literature

Once the disease becomes metastatic, overall survival decreases dramatically. Accordingly, many drugs have been studied in M0CRPC.[7]

Bone-targeted agents like clodronate, zoledronic acid, and denosumab have not shown reliable results. Denosumab was evaluated in a phase III trial, including 1432 CRPC patients, randomized to receive 120 mg denosumab or placebo every four weeks. Denosumab showed an increase in bone metastasis-free survival of 4.2 months [29.5 versus 25.2 months, the hazard ratio (HR) 0.85 p=0.028]. Similarly, it increased the median time to first bone metastasis by 3.7 months (p=0.032).[3] Nevertheless, it is not approved in this scenario, given its adverse effects profile compared with a modest benefit.

Abiraterone, an inhibitor of cytochrome P450 17A1 (CYP17A1) that impairs AR signaling by inhibiting both the 17α-hydroxylase and 17,20-lyase activities of the CYP17A1 enzyme;[12] is prescribed in high-risk metastatic hormone-naive prostate cancer and also in mCRPC. Still, its advantage in M0CRPC has not been demonstrated. The trial IMAGEEN, exposed M0CRPC patients to treatment with 1000 mg of abiraterone plus 5 mg of prednisolone in 28 days cycles, they only found a 50% reduction on PSA levels by the end of the sixth cycle in 86.9% of the patients. However, no comparison group was assessed.[13]

Apalutamide antagonizes the ligand-binding domain of the androgen receptor (AR) with strong affinity, prevents AR nuclear translocation, and does not have agonistic effects in the presence of AR overexpression.[14] The SPARTAN, a double-blind, placebo-controlled, phase 3 trial, included 1207 patients who were randomly assigned, in a 2:1 ratio to receive 240 mg/per day of apatulamide plus ADT vs. placebo plus ADT. Patients at high risk for disease progression (PSA doubling time of ≤10 months) showed a median metastasis-free survival of more than two years longer in the treatment group (40.5 months vs. 16.2 months HR 0.45, 95 % CI 0.32 to 0.63, p= <0.001).[15]

Likewise, PROSPER, another phase III clinical trial, randomized a total of 1401 patients in a 2:1 ratio to Enzalutamide 160 mg/per day plus ADT vs. ADT only. The risk of metastatic progression was decreased by 71 %, with a median metastasis-free survival of 36.6 months versus 14.7 months in the placebo group. Enzalutamide treatment also prolonged both time to first anti-neoplastic treatment (39.6 vs. 17.7 months; HR, 0.21; P < 0.0001) by 22 months and time to PSA progression (37.2 vs. 3.9 months, HR, 0.07; P < 0.0001).

On the other hand, Enzalutamide has also revealed benefits compared to first-generation antiandrogens in the treatment of M0 and metastatic castration resistance prostate cancer (mCRPC). A multicenter, randomized, double-blind phase II trial (STRIVE), compared Enzalutamide 160 mg/day versus Bicalutamide 50 mg/day in patients with M0CRPC and mCRPC. It resulted in a 76 % reduction in mortality and radiological progression in the enzalutamide group. As well as a median progression-free survival (PFS) of 19.4 months versus 5.7 months with bicalutamide.

In another study, ARAMIS, a randomized, double-blind, placebo-controlled, phase 3 trial, enrolled men with M0CRPC and PSADT of 10 months or less. One thousand five hundred nine patients were randomly assigned in a 2:1 ratio to receive darolutamide 600 mg twice daily or placebo while continuing ADT. This trial also found a statistically significant increase in mean metastasis-free survival (40.4 months vs. 18.4 months HR 0.41; 95 % CI 0.34 to 0.50; P<0.001) in addition to benefits concerning all secondary endpoints.[9]

Studies comparing available interventions for the treatment of patients with castration-resistant non-metastatic prostate cancer have recently been published. Di Nunno *et al.* carried out a meta-analysis to measure the effectiveness of the new drugs available in castration-resistant non-metastatic prostate cancer (enzalutamide, darolutamide and apalutamide), having as an outcome the metastasis-free survival, global survival and the measurement of drug toxicity. No indirect comparison was made between the interventions. They concluded that the administration of these drugs has an impact on metastasis-free survival. There was no conclusion regarding overall survival. In the toxicity analysis, they conclude that treatments can increase toxicity in exposed patients.[4] Additionally, Roviello *et al.* published another meta-analysis with the same objective and similar results to the one published by Di Nunno, giving clear benefit to the new therapies when compared with placebo. Our study carried out indirect measurements in order to define differences between the treatments available options, being clear about the benefit of pharmacological interventions over placebo.[5]

Mori *et al.* carry out a systematic review that has similar results like the study by Kumar *et al.*, which has similar results.[5,6]

Finally, Liu *et al.* published a systematic review and network meta-analysis intending to indirectly compare the available and unavailable interventions for the treatment of patients with castration-resistant non-metastatic prostate cancer. In this work, they included eight studies, included for analysis drugs that are not currently used. Unlike our work, we only include drugs currently available and approved for the treatment of these patients. In the study discussed, the researchers conclude that the three antiandrogens currently available improve metastasis-free survival (apalutamide (hazard ratio [HR]: 0.28, 95 % confidence interval [CI]: 0.23 to 0.35), enzalutamide (HR: 0.29, 95 % CI: 0.24 to 0.35), and darolutamide (HR: 0.42, 95 % CI: 0.35 to 0.50).[7] These results confirm what was previously published in meta-analyzes, and also proposing apalutamide and enzalutamide as possible first-line treatments, and daroluramide as second-line treatment. These results contrast with ours. The comparison favors intervention with enzalutamide HR 1.42 95 % CI (1.07 to 1.85). The comparison of darolutamide versus placebo favors pharmacological intervention: HR 0.41 95 % CI (0.33 to 0.49). Similarly, the benefit of using enzalutamide over placebo is clear: HR 0.29 95 % CI (0.24 to 0.35) based on the HR. We found that apalutamide (HR 0.13) and enzalutamide (HR 0.20) provided a lower risk of metastasis compared with darolutamide (HR 0.66). We did not find differences between apalutamide and enzalutamide.

Strengths and limitations

One of the main limitations is that only 3 studies were found. Currently, indirect comparisons of interventions that have not been previously evaluated offer the opportunity to define the likely best intervention for a specific clinical condition. In our study, we raised the importance of comparing the interventions available for the treatment of castration-resistant non-metastatic prostate cancer. This clinical condition has been a source of research, and in the last two years, new interventions have been arranged that have the same utility. However, we do not know which one may be superior to the other. The results we found su-

ggest an answer to this question. We consider that the research question was relevant, mainly when all studies use patients with the same disease stage.

Perhaps, the main limitation is that the validity is based on assumptions, even when the included studies are of good quality, with low variability between them and with low risk of bias. More studies should be carried out to obtain more data for analysis.

Conclusions

We found that CRPC apalutamide and enzalutamide in non-metastatic patients provide a lower risk of metastasis compared with darolutamide. Also, there were no differences between apalutamide and enzalutamide. Therefore, we suggest using any of these two molecules to treat these patients to prevent the presence of metastasis.

Compliance with Ethical Standards

Ethics Statement This systematic review and meta-analysis accomplish all the ethics requirements according to the Helsinki declaration and all international statements.

CRediT Taxonomy

1. **Iregui Parra, JD:** Conceptualization, Methodology, Data curation, Writing - Original draft, Review, and editing.
2. **García Perdomo HA:** Conceptualization, Methodology, Data curation, Writing - Original draft, Proofreading and editing.

Conflict of interest

None of the authors have any conflicts of interest or financial ties to disclose.

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Appendix 1. Search Strategies

Medline (Ovid).

(exp Prostatic Neoplasms or (prostatic adj2 malignanc*).mp or (prostatic adj2 cancer).mp or (Castration Resistant Prostatic Cancer).mp or Exp Prostatic Neoplasms, Castration-Resistant or (Androgen-Independent Prostatic Neoplasm*).mp or (Androgen-Independent Prostatic cancer).mp or (Androgen-Insensitive Prostatic Neoplasm*).mp or (Androgen-Insensitive Prostatic cancer).mp or (Hormone Refractory Prostatic Cancer).mp) AND (apalutamide.mp or exp abiraterone acetate or Abiraterone.mp or (MDV*3100).mp or Enzalutamide.mp or Darolutamide.mp) AND (randomized controlled trial.pt or controlled clinical trial.pt or randomized.ab or placebo.ab or randomly.ab or trial.ab or (clinical adj2 trial).mp or (randomi*ed adj2 controlled adj2 trial).mp or exp double-blind method)

Embase through Scopus

TITLE-ABS-KEY("Prostatic Neoplasm*" or "prostatic malignanc*" or "prostatic cancer" or "Castration Resistant Prostatic Cancer" or "Androgen-Independent Prostatic Neoplasm*" or "Androgen-Independent Prostatic cancer" or "Androgen-Insensitive Prostatic Neoplasm*" or "Androgen-Insensitive Prostatic cancer" or "Hormone Refractory Prostatic Cancer") AND TITLE-ABS-KEY(apalutamide or "abiraterone acetate" or Abiraterone or "MDV*3100" or Enzalutamide or Darolutamide) AND TITLE-ABS-KEY("randomized controlled trial" or "controlled clinical trial" or randomized or placebo or randomly or trial or "clinical trial" or "randomi*ed controlled trial" or "double-blind method")

Central (OVID).

(exp Prostatic Neoplasms or (prostatic adj2 malignanc*).mp or (prostatic adj2 cancer).mp or (Castration Resistant Prostatic Cancer).mp or Exp Prostatic Neoplasms, Castration-Resistant or (Androgen-Independent Prostatic Neoplasm*).mp or (Androgen-Independent Prostatic cancer).mp or (Androgen-Insensitive Prostatic Neoplasm*).mp or (Androgen-Insensitive Prostatic cancer).mp or (Hormone Refractory Prostatic Cancer).mp) AND (apalutamide.mp or exp abiraterone acetate or Abiraterone.mp or (MDV*3100).mp or Enzalutamide.mp or Darolutamide.mp)