SCIE DOI: 10.14744/scie.2025.65768
South. Clin. Ist. Euras. 2025;36(2):150-154

Original Article

The Potential Synergistic Effects of Metformin and Enzalutamide in the Treatment of Metastatic Castration-Resistant Prostate Cancer

Heves Sürmeli,[1] Goncagül Akdağ Topal[2]

[1]Department of Medical Oncology, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye
[2]Department of Medical Oncology,Tokat State Hospital, Tokat, Türkiye

Submitted: 22.03.2025
Revised: 02.05.2025
Accepted: 08.05.2025

Correspondence: Heves Sürmeli, Department of Medical Oncology, Kartal Dr. Lütfi Kırdar City Hospital, Istanbul, Türkiye
E-mail: hevessurmeli@hotmail.com

Keywords: Castration resistant prostate cancer; enzalutamide; metformin.

ABSTRACT

Objective: The primary objective is to investigate the potential synergistic effects of concurrent metformin administration alongside enzalutamide therapy in patients with metastatic castration-resistant prostate cancer (mCRPC). The study aims to uncover novel mechanisms that could lead to enhanced treatment outcomes, including more durable responses, delayed disease progression, and prolonged survival. This exploration seeks to provide critical insights that could expand the therapeutic options available for mCRPC patients.

Methods: This retrospective study evaluated the impact of metformin on progression-free survival (PFS) in 92 patients with mCRPC who received second-line enzalutamide. Patients were divided into two groups: 65 Received enzalutamide alone, while 27 were treated with both enzalutamide and metformin. The primary endpoint was PFS. Statistical analyses, including Kaplan-Meier survival analysis and log-rank tests, were used to compare PFS between the two cohorts, aiming to assess the benefits of metformin in this treatment context.

Results: The analysis revealed that the mean survival time for the enzalutamide-only group was 23 months, while the mean for the enzalutamide-plus-metformin group was 18 months. However, the log-rank test showed no statistically significant difference between the two groups, suggesting that these trends may not indicate a true difference in treatment effectiveness. The median survival times were both 12 months for each treatment cohort, further emphasizing the lack of significant improvement in progression-free survival with the addition of metformin.

Conclusion: This retrospective study explored the effects of adding metformin to enzalutamide therapy in patients with mCRPC after docetaxel treatment. Although mean survival times suggested a potential benefit for the combination, statistical analysis revealed no significant differences in median survival between the two groups. These findings may be influenced by biases inherent in the retrospective design and the small sample size. Thus, further research with larger cohorts and longer follow-up is needed to rigorously evaluate the benefits of the metformin-enzalutamide combination in managing mCRPC.

INTRODUCTION

One promising avenue of research is to explore the potential synergistic effects of concurrent metformin administration on treatment outcomes for patients with metastatic castration-resistant prostate cancer (mCRPC) who are receiving enzalutamide therapy. Metformin, a widely prescribed medication for diabetes, has demonstrated encouraging anti-cancer properties in various preclinical and clinical investigations, suggesting it may provide additional therapeutic benefits when used alongside other cancer therapies.[1-4] By thoroughly investigating the combined effects of metformin and enzalutamide in the management of metastatic castration-resistant prostate cancer (mCRPC), researchers may uncover invaluable insights and opportunities to significantly enhance the efficacy of current treatment approaches. This line of inquiry holds the potential to meaningfully improve clinical outcomes for this patient population, who often face an exceedingly poor prognosis and limited therapeutic options. Through a comprehensive exploration of the synergistic potential between these two agents, researchers may elucidate novel

Table 1. Case processing summary

DM	Group	Total N	Events	Censored	Censored (%)
No	Enza	65	45	20	30.8
Yes	Enza	27	20	7	25.9

DM: Diabetes Mellitus (Yes=With Diabetes, No=Without Diabetes).

mechanisms by which the concurrent administration of metformin and enzalutamide could lead to more durable responses, delayed disease progression, and prolonged survival for individuals battling this advanced and aggressive form of prostate cancer.[5,6] Uncovering such synergistic effects could represent a critical step forward in expanding the therapeutic arsenal and improving the dismal outlook for mCRPC patients, who are in desperate needof more effective treatment strategies to combat this devastating disease. Metformin, a widely used medication for diabetes, has shown promising anti-cancer properties in numerous preclinical and clinical studies, suggesting it may offer synergistic benefits when combined with other cancer therapies. This finding is particularly relevant for the management of metastatic castration-resistant prostate cancer (mCRPC), as this advanced stage of the disease often proves resistant to standard treatments and carries a poor prognosis.

The potential synergistic effects of metformin and enzalutamide, an androgen receptor inhibitor, warrant thorough investigation in the context of mCRPC. By exploring the combined impact of these two agents, researchers may uncover novel mechanisms by which the concurrent administration of metformin and enzalutamide could lead to more durable responses, delayed disease progression, and prolonged survival for individuals battling this aggressive form of prostate cancer.[7,8] Uncovering such synergistic effects could represent a critical step forward in expanding the therapeutic arsenal and improving the dismal outlook for mCRPC patients, who are in desperate need of more effective treatment strategies to combat this devastating disease.

MATERIALS AND METHODS

The study was approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 26/02/2025, No: 2025/010.99/13/1) and complied with the Declaration of Helsinki.

This retrospective study included a total of 92 patients with metastatic castration-resistant prostate cancer, categorized based on whether they received enzalutamide alone or in combination with metformin.

The study's primary endpoint was progression-free survival, measured as the time from the start of second-line enzalutamide therapy to disease progression or death.

The study evaluated treatment outcomes using statistical methods, including Kaplan-Meier survival analysis and log-rank tests, to compare progression-free survival between the two patient cohorts.

Clinical Data Collection

The clinical data for this retrospective study were meticulously gathered from the comprehensive patient medical records maintained at our institution. This data encompassed a wide range of pertinent information, including patient demographics, details of treatment approaches utilized, comorbid conditions, and outcomes directly related to the progression of metastatic castration-resistant prostate cancer. The records were thoroughly examined and cross-referenced to ensure the collection of comprehensive and accurate data, providing a robust foundation for the subsequent analyses.

Statistical Analysis

The primary aim of the statistical analysis was to rigorously compare progression-free survival between patients who received enzalutamide alone and those who received a combination of enzalutamide and metformin. To achieve this, the researchers employed two key statistical approaches:

First; they generated Kaplan-Meier curves to provide a visual representation and comparison of the progression-free survival patterns between the two treatment groups (Table 1). The log-rank test was then utilized to assess the statistical significance of any observed differences in progression-free survival between the enzalutamide-only and enzalutamide-plus-metformin cohorts (Table 2).

Second; the researchers employed a Cox proportional hazards regression model to further evaluate the hazard ratio associated with the combination of enzalutamide and metformin. This approach allowed the researchers to adjust for potential confounding factors, such as patient age, disease burden, and prior treatments, to more accurately

Table 2. Pairwise comparisons

DM	Group	Log-Rank Chi-Square	p-value
No	Enzalutamide	0.019	0.891
Yes	Enzalutamide	2.566	0.109

DM: Diabetes Mellitus (Yes=With Diabetes, No=Without Diabetes).

Table 3. Means and medians for survival time

DM	Group	Mean Survival	Mean Std. Error	Median Survival	Median Std. Error
No	Enza	18.469	2.534	12.6	1.656
Yes	Enza	23.329	4.474	17.17	4.05

DM: Diabetes Mellitus (Yes = With Diabetes, No = Without Diabetes).

determine the impact of the metformin and enzalutamide combination on progression-free survival (Table 3).

The statistical analyses were meticulously conducted using R version 4.1.2, with a significance level of $p<0.05$ to ensure a robust and reliable evaluation of the data.

RESULTS

The mean survival time for the enzalutamide-only group was 23 months, while that of the enzalutamide-plus-metformin group was slightly lower at 18 months (Fig. 1). The overall median survival times were not significantly different between the two treatment groups, with both the enzalutamide-alone and the enzalutamide-plus-metformin cohorts exhibiting a median survival of 12 months. This finding was observed despite the trends suggesting potentially better outcomes in the enzalutamide-only group. While the mean survival times hinted at a potential advantage for the enzalutamide-only approach, the lack of statistical significance in the log-rank test analysis indicates that this observed difference may not reflect a true underlying survival benefit. (Fig. 2) The similarity in median survival between the two treatment arms suggests that the concurrent use of metformin with enzalutamide did not confer a clear and consistent improvement in progression-free survival for this patient population. These results underscore the need for further research, as the retrospective nature of the study and potential confounding factors may have influenced the findings. Larger prospective studies with extended follow-up would be crucial to more definitively evaluate the impact of adding metformin to enzalutamide therapy in the management of metastatic castration-resistant prostate cancer.

The findings indicate that the concurrent administration of metformin may not lead to a statistically significant enhancement in progression-free survival for patients with metastatic castration-resistant prostate cancer receiving second-line enzalutamide therapy.

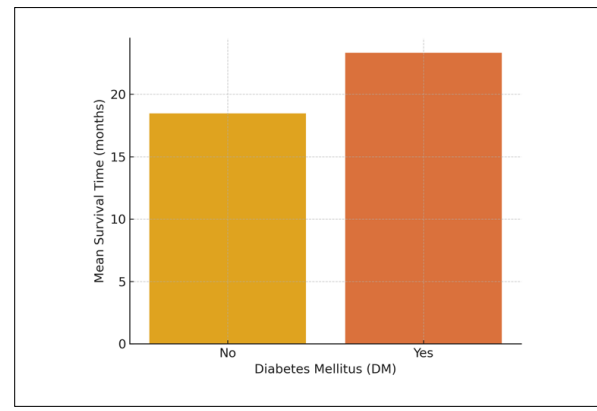

Figure 1. Mean survival by diabetes status (Enzalutamide Group).

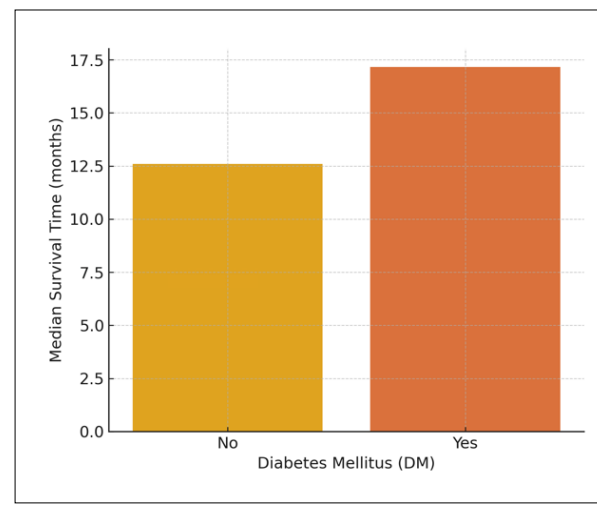

Figure 2. Median survival by diabetes status (Enzalutamide Group).

DISCUSSION

The findings of this retrospective analysis suggest that concurrent use of metformin may be associated with potential improvements in mean survival times for patients with metastatic castration-resistant prostate cancer receiving second-line enzalutamide therapy. The mean survival time for patients receiving both enzalutamide and metformin was 23 months, compared to 18 months for those treated with enzalutamide alone. This trend indicates a possibility of enhanced survival outcomes when combining metformin with enzalutamide. However, the impact on progression-free survival did not demonstrate statistical significance when directly compared to enzalutamide alone. The lack of statistical significance in the log-rank test analysis warrants a cautious interpretation of these observed trends.[9,10] While the data suggests a potential survival benefit for the enzalutamide-plus-metformin cohort[11,12] the absence of statistical significance implies that the observed difference in mean survival may

not represent a true underlying difference in treatment effectiveness between the two groups.[13-16] Further investigation with larger sample sizes and extended follow-up periods would be crucial to more definitively evaluate the potential survival advantages of combining metformin with enzalutamide in the management of metastatic castration-resistant prostate cancer.

The lack of a statistically significant difference may be attributable to limitations inherent to the retrospective study design, as well as potential confounding factors not accounted for in the analyses. The small sample size of the retrospective study may have been insufficient to reliably detect a meaningful difference in treatment outcomes between the groups. The retrospective nature of the data collection could also introduce potential biases, as the researchers had limited control over the selection of patients and the completeness of data. Factors such as patient demographics, disease characteristics, prior treatments, and concurrent medical conditions may not have been evenly distributed between the treatment arms, potentially confounding the analysis. Additionally, the retrospective design limits the ability to ensure consistent data collection and follow-up across all participants. These inherent limitations of retrospective studies underscore the need for well-designed prospective investigations to more conclusively evaluate the impact of adding metformin to enzalutamide therapy in the management of metastatic castration-resistant prostate cancer.[14,15,17]

Further research with larger patient samples and extended follow-up periods may be necessary to more conclusively determine whether combining metformin with enzalutamide provides meaningful benefits for treating metastatic castration-resistant prostate cancer (mCRPC). While the initial findings of this retrospective analysis suggested potential survival advantages associated with the combination therapy, the lack of statistical significance in the key analyses warrants a cautious interpretation of these observed trends. The absence of a statistically significant difference in progression-free survival between the enzalutamide-alone and enzalutamide-plus-metformin groups indicates that the addition of metformin may not consistently or reliably improve clinical outcomes for mCRPC patients receiving second-line enzalutamide therapy.

Well-designed prospective clinical trials with larger patient cohorts and longer follow-up durations would be crucial to more definitively elucidate the impact of metformin on treatment outcomes when used in combination with enzalutamide for managing mCRPC. Such rigorous prospective investigations would enable researchers to better control for potential confounding factors and more accurately ascertain whether the metformin-enzalutamide combination confers meaningful survival or other clinical benefits beyond enzalutamide monotherapy in this challenging patient population.

Conclusion

This retrospective study examined the impact of adding metformin to enzalutamide therapy in patients with metastatic castration-resistant prostate cancer (mCRPC) who had previously received docetaxel treatment. While the mean survival times suggested a potential for longer survival among those receiving the enzalutamide-metformin combination, the lack of statistical significance in the log-rank test analysis requires a cautious interpretation of these results. The median survival times also did not demonstrate significant differences between the two treatment groups, implying that the addition of metformin may not confer a clear advantage in extending progression-free survival alongside enzalutamide therapy in this mCRPC patient population. The lack of a statistically significant difference between the treatment groups may be attributed to several factors. The retrospective nature of the study design introduces potential biases, as the researchers had limited control over patient selection and data completeness. Factors such as patient demographics, disease characteristics, prior treatments, and concurrent medical conditions may not have been evenly distributed between the groups, potentially confounding the analysis. Additionally, the small sample size of the study may have been insufficient to reliably detect a meaningful difference in treatment outcomes. The key strength of the study lies in its novel focus on a therapeutic combination supported by plausible mechanistic rationale. However, the lack of statistical power, absence of molecular stratification, and real-world variability limit the generalizability of results. Nonetheless, further research with larger patient cohorts and extended follow-up periods may be necessary to more definitively evaluate the potential benefits of the metformin-enzalutamide combination in the management of mCRPC. Despite the observed trends, the findings of this retrospective analysis indicate that the incorporation of metformin does not provide a statistically significant improvement in progression-free survival for mCRPC patients receiving second-line enzalutamide treatment. Well-designed prospective clinical trials would be crucial to better understand the impact of this combination therapy and its suitability for managing this challenging patient population.

Ethics Committee Approval

The study was approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 26.02.2025, Decision No: 2025/010.99/13/1).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: H.S.; Design: H.S.; Supervision: G.A.T.; Materials: G.A.T.; Data: H.S.; Analysis: G.A.T.; Literature search: H.S.; Writing: H.S.; Critical revision: H.S.

Conflict of Interest

None declared.

REFERENCES

1. Hua Y, Zheng Y, Yao Y, Jia R, Ge S, Zhuang A. Metformin and cancer hallmarks: Shedding new lights on therapeutic repurposing. J Transl Med 2023;21:403. [CrossRef]
2. Xie Y, Wang L, Khan MA, Hamburger AW, Guang W, Passaniti A, et al. Metformin and androgen receptor-axis-targeted agents induce two PARP-1-dependent cell death pathways in androgen-sensitive human prostate cancer cells. Cancers (Basel) 2021;13:633. [CrossRef]
3. Morales DR, Morris AD. Metformin in cancer treatment and prevention. Annu Rev Med 2015;66:17–29. [CrossRef]
4. Noto H, Goto A, Tsujimoto T, Noda M. Cancer risk in diabetic patients treated with metformin: A systematic review and meta-analysis. PLoS One 2012;7:e33411. [CrossRef]
5. Fonseca NM, Roberts ME, Wyatt AW. A marrow-minded look at immune checkpoint blockade resistance in metastatic castration-resistant prostate cancer. Transl Androl Urol 2021;10:4009–18. [CrossRef]
6. Dowling RJ, Goodwin PJ, Stambolic V. Understanding the benefit of metformin use in cancer treatment. BMC Med 2011;9:33. [CrossRef]
7. Freedland SJ, Gleave M, De Giorgi U, Rannikko A, Pieczonka CM, Tutrone RF, et al. Enzalutamide and quality of life in biochemically recurrent prostate cancer. NEJM Evid 2023;2(12):EVIDoa2300251. [CrossRef]
8. Sternberg CN, Fizazi K, Saad F, Shore ND, De Giorgi U, Penson DF, et al. Enzalutamide and survival in nonmetastatic, castration-resistant prostate cancer. N Engl J Med 2020;382:2197–206. [CrossRef]
9. Deek MP, Phillips R, Tran PT. Radiotherapy in the management of metastatic hormone-sensitive prostate cancer. Cancer J 2020;26:87–93. [CrossRef]
10. Lei Y, He X, Huang H, He Y, Lan J, Yang J, et al. The efficacy of metformin in prostate cancer: A systematic review and meta-analysis. Clin Transl Oncol 2021;23:2506–16.
11. Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: An overview. Clin Sci (Lond) 2012;122:253–70. [CrossRef]
12. Pollak M. Metformin and other biguanides in oncology: Advancing the research agenda. Cancer Prev Res (Phila) 2010;3:1060–5. [CrossRef]
13. Cuyàs E, Verdura S, Llorach-Parés L, Fernández-Arroyo S, Joven J, Martin-Castillo B, et al. Metformin is a direct SIRT1-activating compound: Implications for the treatment of age-associated disorders. Cell Cycle 2018;17:359–66. [CrossRef]
14. Clinical Trials. Castration compared to castration plus metformin as first line treatment for patients with advanced prostate cancer. Available at: https://clinicaltrials.gov/ct2/show/NCT01620593. Accessed Feb 21, 2025.
15. Wen J, Yi Z, Chen Y, Huang J, Mao X, Zhang L, et al. Efficacy of metformin therapy in patients with cancer: A meta-analysis of randomized controlled trials. BMC Med 2022;20:102. [CrossRef]
16. Gillessen S, Attard G, Beer TM, Beltran H, Bjartell A, Bossi A, et al. Management of patients with advanced prostate cancer: Report of the Advanced Prostate Cancer Consensus Conference 2019. Eur Urol 2020;77:508–47. [CrossRef]
17. Raval AD, Thakker D, Vyas A, Salkini M, Madhavan S, Sambamoorthi U, et al. Impact of metformin on clinical outcomes among men with prostate cancer: A systematic review and meta-analysis. Prostate Cancer Prostatic Dis 2015;18:110–21. [CrossRef]

Metastatik Kastrasyona Dirençli Prostat Kanseri Tedavisinde Metformin ve Enzalutamidin Potansiyel Sinerjik Etkileri

Amaç: Bu araştırmanın amacı, metastatik kastrasyona dirençli prostat kanseri (mKDPK) hastalarında enzalutamid tedavisi yanı sıra metformin kullanımının potansiyel sinerjik etkilerini incelemektir. Bu iki ajanın birleştirilmiş tedavi etkisini inceleyerek, daha uzun süreli yanıtlar, hastalığın ilerlemesinin gecikmesi ve daha uzun sağkalım gibi geliştirilmiş tedavi sonuçlarına yol açabilecek yeni mekanizmaları ortaya çıkarmayı hedeflemektedir. Sonuçta, araştırma klinik sonuçları iyileştirmeyi ve bu agresif prostat kanseri formunun tedavisi için daha etkili stratejiler sunmayı hedeflemektedir.

Gereç ve Yöntem: Bu retrospektif çalışma, daha önceki doksetaksel tedavisini takiben ikinci basamak enzalutamid alan mKDPK hastalarında metforminin progresyonsuz sağkalım (PSK) üzerindeki etkisini değerlendirdi. Hastalar iki gruba ayrıldı: 65'i yalnızca enzalutamid aldı, 27'si ise hem enzalutamid hem de metformin ile tedavi edildi. Birincil sonlanım noktası, ikinci basamak enzalutamid başlangıcından hastalık ilerlemesine veya ölüme kadar ölçülen PSK idi. İki kohort arasındaki PSK'yı karşılaştırmak için Kaplan-Meier sağkalım analizi ve log-rank testleri gibi istatistiksel analizler kullanıldı; bu, bu tedavi bağlamında metforminin faydalarını değerlendirmeyi amaçladı.

Bulgular: Enzalutamid grubunun ortalama sağkalım süresinin 23 ay, enzalutamid ve metformin grubunun ortalamasının ise 18 ay olarak ortaya kondu. Ancak, log-rank testi iki grup arasında istatistiksel olarak anlamlı bir fark göstermedi, bu da tedavi etkinliğinde bir fark olmayabileceğini düşündürdü. Medyan sağkalım süreleri her iki tedavi kohortu için de 12 ay olup, metforminin eklenmesiyle progresyonsuz sağkalımda önemli bir iyileşme olmadığını vurgulamaktadır.

Sonuç: Bu retrospektif çalışma, mKDPK olan ve daha önce doksetaksel tedavisi almış hastalarda enzalutamid tedavisine metformin eklenmesinin etkilerini araştırmıştır. Ortalama sağkalım süreleri, kombinasyon tedavisinin potansiyel bir fayda sağlayabileceğini öne sürse de, istatistiksel analizler her iki grup arasında medyan sağkalım açısından anlamlı bir fark ortaya koymamıştır. Bu sonuçlar, çalışmanın retrospektif yapısı ve sınırlı örneklem büyüklüğü gibi biaslardan etkilenmiş olabilir. Bu nedenle, metformin ve enzalutamid kombinasyonunun mKDPK tedavisindeki etkinliğini daha sağlam bir şekilde değerlendirebilmek için daha büyük hasta gruplarıyla ve daha uzun izlem süreleriyle yapılacak ileri araştırmalara ihtiyaç vardır.

Anahtar Sözcükler: Enzalutamid; kastrasyon dirençli prostat kanseri; metformin.