Redefining Treatment Paradigms in Metastatic Castration-resistant Prostate Cancer: A Comprehensive Analysis of Cabozantinib and Atezolizumab Based on the CONTACT-02 Study Results

Sara Elyas[1] and Ulka Vaishampayan[2]

1. Division of Hematology and Oncology, University of Michigan, Ann Arbor, MI, USA; 2. Lyman Briggs College, Michigan State University, East Lansing, MI, USA

https://doi.org/10.17925/OHR.2024.20.2.3

Metastatic castration-resistant prostate cancer (mCRPC) remains one of the most challenging stages of prostate cancer (PCa) due to its aggressive nature and poor prognosis. Traditional treatments often fail as the disease progresses, necessitating unique therapeutic approaches. This review focuses on the CONTACT-02 study, which evaluated the efficacy of combining cabozantinib and atezolizumab in mCRPC treatment. Cabozantinib targets multiple receptors including mesenchymal–epithelial transition factor, vascular endothelial growth factor receptor and anexelekto involved in tumour growth, angiogenesis and metastasis, while atezolizumab enhances the immune response by inhibiting programmed death-ligand 1. The phase III CONTACT-02 trial compared this combination therapy with a second novel hormonal therapy (NHT) in patients who had progressed following prior NHT. Results showed a significant improvement in median progression-free survival for the cabozantinib plus atezolizumab group (6.3 months) versus the control group (4.2 months), along with a higher overall response rate of 13.6% compared with 4.2%. In addition, subgroups with liver metastasis and those previously treated with docetaxel exhibited even more significant benefits. The combination therapy was associated with a higher incidence of treatment-emergent adverse events, particularly grade 3/4 events, necessitating careful patient selection and management. The findings of the CONTACT-02 study suggest that cabozantinib plus atezolizumab could offer a new therapeutic option for patients with limited alternatives. In conclusion, while the combination of cabozantinib and atezolizumab presents increased risks of adverse events, its potential to improve survival outcomes in patients with mCRPC highlights the importance of continued research and careful clinical application. This review highlights the need for personalized treatment strategies to manage advanced PCa and improve patient outcomes effectively.

Keywords

Atezolizumab, cabozantinib, castration-resistant, immune therapy, liver metastases, metastatic prostate cancer, tyrosine kinase inhibitor therapy

Disclosures: Ulka Vaishampayan has consulted with Exelixis, BMS, Merck and Pfizer. Sara Elyas has no financial or non-financial relationships or activities to declare in relation to this article.

Review process: Double-blind peer review.

Compliance with ethics: This article involves a review of literature and does not report on new clinical data, or any studies with human or animal subjects performed by any of the authors.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Authorship: All named authors meet the criteria of the International Committee of Medical Journal Editors for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval for the version to be published.

Received: 17 September 2024

Accepted: 22 October 2024

Published online: 9 December 2024

Citation: *touchREVIEWS in Oncology & Haematology.* 2024;20(2):45–50

Corresponding author: Dr Ulka Vaishampayan, Department of Medicine, Division of Hematology and Oncology, 7217 Rogel Cancer Center/University of Michigan, 1500 E Medical Center Dr, Ann Arbor, MI 48109, USA. E: vaishamu@med.umich.edu

Support: No funding was received for the publication of this article.

Metastatic castration-resistant prostate cancer (mCRPC) represents the most formidable stage of prostate cancer (PCa) and is responsible for the majority of PCa-related mortalities. This advanced form of the disease typically evolves from less aggressive stages.[1] PCa is broadly categorized into various stages, from early stage to metastatic castration-resistant, each presenting unique clinical challenges. Notably, metastatic hormone-sensitive PCa constitutes a significant portion of new cases each year. It serves as a precursor to mCRPC, highlighting the transition challenges in treatment arising from resistance to hormone therapy.[2]

Introducing new therapeutic agents has shifted the treatment model, providing new management options for mCRPC. However, these therapies also raise economic considerations, as their adoption significantly impacts healthcare budgets.[3] Furthermore, the efficacy of such treatments can be compromised by patient-specific factors such as comorbidities, especially in the elderly, which can profoundly influence treatment outcomes.[4]

A key aspect of mCRPC's pathology is the overexpression of prostate-specific membrane antigen (PSMA), which has catalysed the development of targeted diagnostic and therapeutic strategies. Targeting PSMA through radiopharmaceuticals has shown promise, offering new avenues for diagnosing and combating this advanced cancer stage.[5] Despite these advances, the median survival for patients with mCRPC remains dismally low, highlighting the urgent need for more effective and sustainable treatment modalities.[6]

As resistance to androgen deprivation therapy (ADT) becomes increasingly common, the clinical challenge intensifies, requiring the exploration of new therapeutic strategies to manage this transition effectively. Now the addition of either abiraterone with prednisone, enzalutamide, apalutamide or docetaxel chemotherapy combined with ADT is considered standard treatment for patients with high-risk non-metastatic PCa or metastatic castrate-sensitive PCa. The combination of enzalutamide and abiraterone did not show benefit over single-agent enzalutamide, and these should not be combined. Clinically important improvements in survival from the addition of androgen axis-inhibiting agents to ADT were maintained for longer than 7 years.[7] The majority of patients with metastatic PCa are entering the castrate-resistant phase already pretreated with at least one androgen axis inhibitor and maybe even docetaxel chemotherapy. This makes therapeutic options limited in the castrate-resistant phase.

The evolution of mCRPC involves not just resistance to conventional hormone therapy but also genetic, molecular and cellular mechanisms that drive the cancer's progression and resistance to treatment.[8] Moreover, the aggressiveness of subtypes such as neuroendocrine PCa further complicates treatment, as these are rapidly progressing and highly lethal.[9]

The emergence of new treatment strategies, such as immune checkpoint inhibitors and tyrosine kinase inhibitors, has begun to alter therapeutic approaches. By modifying the immune system and targeting critical cellular pathways, these therapies offer hope for more effective management of this formidable disease.[10,11] Ongoing research into unique therapies, understanding resistance mechanisms and developing new diagnostic modalities are essential for improving patient outcomes with mCRPC.

Cabozantinib and its role in advanced prostate cancer

Mechanism of action

Cabozantinib, an oral tyrosine kinase inhibitor, exerts its therapeutic effects by targeting multiple receptor tyrosine kinases involved in tumourigenesis and cancer progression. Specifically, cabozantinib inhibits key receptors, such as mesenchymal–epithelial transition factor (MET), vascular endothelial growth factor receptors (VEGFRs) and anexelekto (AXL), which are crucial in promoting tumour growth, angiogenesis, metastasis and drug resistance.[12] By targeting these receptors simultaneously, cabozantinib offers a comprehensive approach to disrupting cancer cell signalling pathways and inhibiting tumour progression. MET, a hepatocyte growth factor receptor, is known to promote cell proliferation, survival and migration in various cancers, including PCa.[13] Cabozantinib's inhibition of MET signalling interferes with these processes, suppressing tumour growth and metastasis. In addition, cabozantinib targets VEGFRs, essential for angiogenesis.[14] By blocking VEGFR signalling, cabozantinib inhibits angiogenesis, depriving tumours of the necessary blood supply for their growth and spread. Moreover, cabozantinib's inhibition of AXL, a receptor tyrosine kinase associated with cancer cell survival, invasion and resistance to therapy, further enhances its anti-cancer effects.[15] AXL activation has been linked to the development of resistance to targeted therapies, making it a critical target for overcoming treatment resistance in various cancers, including renal cell carcinoma.[16] By blocking AXL signalling, cabozantinib can potentially overcome resistance mechanisms and improve treatment outcomes in patients with advanced cancers. In preclinical studies, the inhibition of key receptors by cabozantinib has been shown to induce tumour regression, inhibit angiogenesis and suppress metastatic potential in various cancer models.[17]

The ability of cabozantinib to modulate the tumour microenvironment and promote an immune-permissive state further enhances its therapeutic efficacy.[18] By inducing immunogenic stress in cancer cells and modulating immune responses, cabozantinib may enhance the anti-tumour immune response and improve treatment outcomes in patients with advanced cancers.

Previous uses of cabozantinib

Cabozantinib has demonstrated clinical effectiveness across a spectrum of tumour types, achieving the Food and Drug Administration's (FDA) approval in metastatic renal cell carcinoma, hepatocellular carcinoma, medullary thyroid cancer and gastrointestinal stromal tumours.[19] Given its inhibition of critical signalling pathways, this clinical versatility suggests a robust mechanistic action.

The scope of cabozantinib's efficacy extends beyond its currently approved indications to include other challenging conditions such as castration-resistant PCa, urothelial carcinoma and non-small-cell lung cancer.[20] Particularly, cabozantinib effectively inhibits MET phosphorylation in non-small-cell lung cancer cells, a key driver in cancer progression, thereby reducing downstream signalling via protein kinase B and extracellular signal-regulated kinase, vital for cell survival and proliferation.[13,20] Clinical evaluation is ongoing in multiple malignancies.

The toxicities of cabozantinib need to be judiciously managed. Patient and caregiver education and anticipation of toxicities are key components of this therapy. Although treatment breaks in these patients could reasonably be considered, caution should be exercised since it may impact efficacy, as seen in the STAR trial ('A Randomised Multi-stage Phase II/III Trials of Standard First-line Therapy [Sunitinib or Pazopanib] Comparing Temporary Cessation with Allowing Continuation, in the Treatment of Locally Advanced and/or Metastatic Renal Cancer'; ClinicalTrials.gov identifier: NCT01391106), conducted in advanced kidney cancer.[21]

The evidence of its encouraging activity in metastatic castrate-resistant PCa underscores its potential in addressing treatment-resistant forms of cancer.[22] Its potent anti-c-ros oncogene 1 (ROS1) activity in various solid malignancies highlights its potential as a versatile agent capable of targeting diverse oncogenic drivers.[23] Moreover, recent studies suggest that cabozantinib not only acts directly on tumour cells but may also modify the tumour microenvironment. It has been shown to influence the immune response by impacting dendritic and natural killer cells, potentially enhancing the efficacy of immune checkpoint blockers.[24] This dual mechanism of action, both directly against tumour cells and indirectly through immunomodulation, provides a compelling rationale for its use in a broad range of oncological applications.

Rationale for use in prostate cancer

The rationale for integrating cabozantinib into the therapeutic regimen for advanced PCa is built by its multi-targeted mechanism that aligns well with the pathology of mCRPC. The inhibition of MET and VEGFR not only impacts tumour growth and vascularization but also addresses the bone metastases that frequently complicate PCa progression.[25,26] By disrupting these pathways, cabozantinib could theoretically reduce tumour viability and metastatic spread, crucial outcomes for patients with mCRPC who often face limited treatment options. Moreover, the drug's ability to modulate the immune environment, enhancing the efficacy of immunotherapies, presents an innovative approach to treatment, potentially overcoming some of the traditional resistances encountered

with other therapies.[27] Clinical and preclinical studies support the application of cabozantinib in PCa, showing promising results in tumour regression and inhibition of angiogenesis, thus providing a compelling case for its use in advanced stages of the disease.[28,29] Randomized trials, however, have been unable to demonstrate significant incremental efficacy over the standard of care in mCRPC. The CONTACT-02 study ('A Study of Cabozantinib in Combination with Atezolizumab Versus Second Novel Hormonal Therapy in Subjects with Metastatic Castration-resistant Prostate Cancer'; ClinicalTrials.gov identifier: NCT04446117) evaluated cabozantinib plus atezolizumab in comparison with a second novel hormonal therapy (NHT) in chemo-naive mCRPC.

Results

Overview of the CONTACT-02 study

The CONTACT-02 study is a pivotal phase III clinical trial evaluating the efficacy and safety of cabozantinib in combination with atezolizumab versus second NHT in patients with mCRPC who have progressed following prior NHT.[30] This study addresses a critical need for effective treatment options in patients with mCRPC having extra pelvic nodal or visceral metastasis, a group known to have poor prognosis with limited treatment alternatives beyond chemotherapy. Patients were randomized in a 1:1 ratio to receive either cabozantinib plus atezolizumab or control treatments, which included abiraterone plus prednisone or enzalutamide. Key eligibility criteria included disease progression on one prior NHT, measurable disease and an Eastern Cooperative Oncology Group performance status of ≤1.[30]

Summary

- Progression-free survival (PFS): The median PFS was significantly longer in the cabozantinib plus atezolizumab group compared with the control group (6.3 versus 4.2 months; hazard ratio [HR] 0.65; 95% confidence interval [CI] 0.50–0.84; p=0.0007). Notably, the PFS benefit was even more pronounced in subgroups with liver metastasis (6.0 versus 2.1 months; HR 0.47; 95% CI 0.30–0.74) and in those who had previously received docetaxel for metastatic castration-sensitive PCa (8.8 versus 4.1 months; HR 0.55; 95% CI 0.32–0.96).[30]
- Overall response rate (ORR) and duration of response (DOR): The ORR was higher in the cabozantinib plus atezolizumab group compared with the control group among patients with follow-up of at least 6 months (13.6 versus 4.2%). The median DOR was 9.7 months for cabozantinib plus atezolizumab, whereas it was not reached in the control group. In addition, the time to respond was quicker in the treatment group compared with the control group (2.3 versus 4.6 months).[30]
- Treatment-emergent adverse events (TEAEs): High rates of TEAEs were observed in both groups, with 97% in the cabozantinib plus atezolizumab group and 87% in the control group. However, grade 3/4 events were more common in the treatment group (48 versus 23%). The most common grade 3/4 adverse events in the cabozantinib plus atezolizumab group include fatigue, hypertension, diarrhoea and hepatotoxicity. These side effects significantly contributed to treatment discontinuation. No grade 5 treatment-related adverse events occurred in either group. Treatment discontinuation due to adverse events was noted in the two groups (13% in cabozantinib plus atezolizumab versus 2% in control).[30]

Key outcomes

Table 1 presents a comparative analysis of PFS, ORR, DOR and TEAEs between patients treated with cabozantinib plus atezolizumab (n=253) and those receiving second NHT as control (n=254). Data are highlighted for the total study population and specific subgroups, demonstrating the enhanced efficacy and safety profile of the treatment combination, particularly in patients with liver metastasis and those previously treated with docetaxel. Statistical significance is noted where applicable to emphasize findings relevant to clinical practice.[30]

Discussion

Clinical implications

The results of the CONTACT-02 study mark a significant advancement in the treatment landscape for mCRPC, particularly for patients with extra pelvic nodal or visceral metastases. Historically, this patient group has faced poor prognosis with limited treatment options beyond chemotherapy. The finding of the study that cabozantinib in combination with atezolizumab significantly extends PFS compared with NHT suggests a significant shift in therapeutic strategies (HR 0.65; 95% CI 0.50–0.84; p=0.0007). This improvement in PFS was even more pronounced among subgroups with historically difficult-to-treat characteristics, such as liver metastases (HR 0.47; 95% CI 0.30–0.74) and those previously treated with docetaxel (HR 0.55; 95% CI 0.32–0.96).[30]

These results are significant, given that cabozantinib promotes an immune-permissive tumour environment, which may enhance the response to immune checkpoint inhibitors such as atezolizumab. The combination's ability to inhibit multiple key pathways involved in tumour growth and resistance, such as MET, VEGFR and AXL, provides a robust mechanism for tackling the complex biology of mCRPC, contributing to the observed clinical benefits.[30]

Potential benefits and risks

The potential benefits of cabozantinib plus atezolizumab extend beyond merely improving median PFS. The ORR observed with the combination therapy (13.6 versus 4.2% in the control group) indicates a substantial proportion of patients achieving a significant reduction in tumour burden. In addition, the median DOR and quicker time to respond compared with controls suggest that not only do more patients respond to treatment but they also do so more rapidly and with sustained effects, enhancing the quality of life and potentially delaying the progression to symptomatic stages.[30]

However, these clinical benefits come with associated risks. The TEAEs were notably higher in the combination therapy group (97 versus 87% in controls), with a significant increase in grade 3/4 events (48 versus 23%). This underscores the necessity for careful patient selection and management strategies to mitigate these risks. The high rate of adverse events necessitates vigilant monitoring and possibly pre-emptive management of side effects to maintain patient quality of life and adherence to therapy.[30]

The CONTACT-02 study demonstrates that cabozantinib plus atezolizumab could represent an addition to the treatment arsenal for mCRPC, particularly for patients with challenging prognostic features such as liver metastases. While the increase in TEAEs requires attention, the potential for significantly improved outcomes may justify these risks for many patients. Ongoing follow-up for overall survival (OS) will be crucial to fully establish this treatment's long-term benefits and positioning within the mCRPC therapeutic landscape. This study highlights the modest efficacy of combining tyrosine kinase inhibitors with immune checkpoint inhibitors but also sets the stage for future research into optimizing combination therapies to balance effectiveness and safety.[30]

Table 1: Summary of key outcomes from the CONTACT-02 study comparing cabozantinib plus atezolizumab versus control in patients with metastatic castration-resistant prostate cancer[30]

Key parameters	No. of patients	CONTACT-02 study (cabozantinib + atezolizumab)	Control group (second NHT)	Statistical significance
Median PFS	253/254	6.3 months	4.2 months	HR 0.65; 95% CI 0.50–0.84; p=0.0007
Median overall survival Immature, median follow-up for 12 months	253/254	16.7 months	14.6 months	HR 0.79; 95% CI 0.58–1.07; p=0.13
PFS in patients with liver metastasis	51/48	6.2 months	2.1 months	HR 0.43; 95% CI 0.27–0.78
Liver metastases median OS Immature, median follow-up for 12 months	59/60	16.4 months	9.8 months	HR 0.6; 95% CI 0.35–1.02
Median PFS previously treated with docetaxel for mCSPC	45/44	8.8 months	4.1 months	HR 0.55; 95% CI 0.32–0.96
Median OS Pretreated with docetaxel in mCSPC	57/58	20.9 months	11.3 months	HR 0.56; 95% CI 0.5–0.88
Median PFS Bone metastases	162/155	6.3 months	4.1 months	HR 0.67; 95% CI 0.29–1.08
Median OS Bone metastases	206/196	16.4 months	11.4 months	HR 0.74; 95% CI 0.54–1.02
ORR	-	13.6%	4.2%	-
Median DOR	-	9.7 months	Not reached	-
Time to response	248/253	2.3 months	4.6 months	-
TEAEs – any grade	248/253	97%	87%	-
Grade 3/4 TEAEs	248/253	48%	23%	-
Discontinuation due to TEAEs for any therapy component	248/253	13%	2%	-
Discontinuation due to TEAEs for all therapy components	248/253	5%	2%	-

CI = confidence interval; DOR = duration of response; HR = hazard ratio; mCSPC = metastatic castration-sensitive prostate cancer; NHT = novel hormonal therapy ; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; TEAEs = treatment-emergent adverse events.

The treatment landscape in metastatic castration-resistant prostate cancer

Numerous therapies have shown benefits in mCRPC and are available for use. However, therapeutic selection remains challenging, and better biomarkers are needed to guide therapy. A key aspect of mCRPC's pathology is the overexpression of PSMA, which has catalysed the development of targeted diagnostic and therapeutic strategies. It is also worth mentioning that there is significant interest in integrating image-based information from radiomics into the multiomics framework, aiming to combine biomolecular-level information with imaging data. The clinical application of radiomics involves identifying the relationship between the features extracted from images and the clinical outcome of interest. In PCa, common imaging modalities include magnetic resonance imaging, transrectal ultrasound, conventional computed tomography (CT), cone-beam CT and molecular imaging, often in the form of positron emission tomography/CT with tracers such as radiolabelled PSMA and fluorine-labelled 18F-choline.[31] The proven clinical efficacy and FDA approval of PSMA Lu177 are the start of molecular therapeutics in the field of advanced PCa. However, biomarker applications need to be better studied, and a sizeable proportion of patients were either not eligible for the study due to non-PSMA-avid disease or derived minimal benefit.

The emergence of new treatment strategies, such as immune checkpoint inhibitors and tyrosine kinase inhibitors, has begun to alter therapeutic approaches. The germline or somatic aberrations in the DNA damage repair genes are found in 19% of primary PCa and almost 23% of mCRPC and compromise genomic integrity. As such, several poly(ADP-ribose) polymerase inhibitors have been investigated in patients with mCRPC and are effective in germline breast cancer gene 2 (BRCA2) mutants. Patients with BRCA2 pathogenic sequence variants have increased levels of serum prostate-specific antigen (PSA) at diagnosis, an increased proportion of high Gleason tumours, elevated rates of nodal and distant metastases and high recurrence rates.[32] In the CONTACT-02 study, no genomic sequencing was conducted or available, and this can result in a major imbalance within the arms of the trial. The incidence of DNA repair mutations is likely higher in this measurable disease subgroup, representing aggressive disease, especially with liver metastases.

The introduction of cabozantinib plus atezolizumab into the treatment plan for mCRPC offers a notable divergence from the efficacy and safety profiles of existing standard therapies. Standard options such as abiraterone, enzalutamide and chemotherapy have historically defined mCRPC management but often come with limitations concerning efficacy in specific patient subsets and cumulative toxicities. The CONTACT-02 study highlights a crucial advantage of combination therapy over NHT, particularly in extending PFS and improving response rates among patients who have previously shown progression on NHTs.

Notably, the dual inhibition strategy targeting both tumour growth and the immune microenvironment may address some key pathways

contributing to resistance in mCRPC. In contrast, standard therapies often target singular pathways, which might explain the improved outcomes observed with cabozantinib plus atezolizumab. However, the safety profile of this combination, marked by a higher incidence of grade 3/4 adverse events, suggests a trade-off that may limit its use to patients who can tolerate more intensive treatment regimens. This aspect may necessitate a more nuanced patient selection process compared with therapies such as enzalutamide or abiraterone, which are generally well tolerated.

Future directions

The promising results of the CONTACT-02 study invite several routes for further research to optimize and expand the use of cabozantinib plus atezolizumab in mCRPC. One immediate area of interest is the need for more extended follow-up periods to ascertain long-term outcomes, particularly OS, which remains immature in the current dataset. Understanding the long-term survival benefits will be crucial for determining the full clinical value of this treatment combination. This study was conducted based on clinical biomarkers of poor prognosis, such as measurable disease requirements and the percentage of patients with liver metastasis who have typically been a minority in most mCRPC studies. Within this patient population with an otherwise dismal prognosis, cabozantinib plus atezolizumab offers the hope of extending time to progression and potential therapeutic prolongation of survival (data not available).

Moreover, exploring biomarkers for efficacy is a critical area for future studies. Identifying predictive biomarkers could enable the stratification of patients most likely to benefit from this treatment, enhancing personalized therapy approaches in mCRPC. This stratification could also help manage the risk-to-benefit ratio more effectively by targeting the treatment to those most likely to respond. Besides validated clinical biomarkers, there are others such as ki-67, circulating tumour cell counts, retinoblastoma loss and miRNA-21 that may contribute to pathogenesis and castration resistance. Serum miRNAs in the miRNA-200 and miRNA-17 families were associated with a PSA response and improved OS in mCRPC receiving docetaxel. The miRNA-200 family of markers is hypothesized to be involved in the regulation of epithelial-to-mesenchymal transition, a mechanism of drug resistance and metastasis, and the miRNA-17 family has potential immune regulatory functions.[33] These miRNA families may be involved in the mechanisms of mCRPC resistance; however, they need validation in a prospective trial.

In addition, further trials in different patient subsets, including those with varying levels of disease progression, prior treatment histories and comorbid conditions, could provide deeper insights into the versatility and adaptability of cabozantinib plus atezolizumab. Trials focusing on patients with specific genetic mutations or molecular profiles of their tumours could also uncover subgroups who may derive even greater benefits or face fewer risks from this therapy.

Lastly, considering the high rate of TEAEs, studies aimed at mitigation strategies, such as dose adjustments or supportive care enhancements, will be essential. These studies could broaden the applicability of cabozantinib plus atezolizumab by making it suitable for a broader range of patients, including those who might otherwise be unable to tolerate its intensive regimen.

Conclusion

In conclusion, the CONTACT-02 study's evaluation of cabozantinib and atezolizumab for treating mCRPC marks a significant milestone in conducting studies for poor-prognosis mCRPC and may lead the way for evaluating therapies specifically for this subset, particularly for forms resistant to conventional treatments. This combination therapy strategically employs cabozantinib's robust inhibition of key pathways – MET, VEGFR and AXL – to thwart tumour growth and metastasis, while atezolizumab's blockade of programmed death-ligand 1 enhances the immune response, forging a dual-front assault on cancer. The clinical outcomes from the study, notably the prolonged PFS and the superior ORR, especially among patients with liver metastases, highlight the therapy's potent efficacy against some of the most challenging mCRPC cases.

However, the significant rate of TEAEs recorded necessitates a careful approach to patient selection, emphasizing meticulous management strategies to balance the potential benefits with the possible risks. This nuanced approach underlines the importance of tailoring treatment to individual patient profiles, a strategy that not only enhances efficacy but also mitigates risks. Judicious monitoring and management of toxicities is required.

The study highlights the poor-risk patient population with mCRPC with a dismal prognosis. It represents the start of focused drug development strategies in mCRPC, which is resistant to currently available therapeutic strategies. Future investigation and follow-up of the cabozantinib plus atezolizumab regimen will yield critical information regarding the regimen's future in mCRPC. ❑

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