# Chemoimmunotherapy Extends PFS in Metastatic Prostate Cancer Subset

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Metastatic castration-resistant prostate cancer (mCRPC) remains a significant clinical challenge, with existing therapies offering incremental benefits. The integration of immunotherapy into treatment paradigms has shown promise in various solid tumours, but its role in prostate cancer has been less defined. A recent investigation into a chemoimmunotherapy combination suggests a potential improvement in progression-free survival (PFS) for a distinct patient population within this disease.

**KEY TAKEAWAYS**

- The Pivot: The addition of an immune checkpoint inhibitor to chemotherapy may offer a PFS advantage in a specific mCRPC patient subgroup.
- The Data: A hazard ratio of 0.72 (95% CI: 0.61-0.85; p=0.0001) for PFS was observed in the overall study population.
- The Action: Clinicians should consider patient selection carefully, particularly for those with specific molecular or clinical characteristics, when evaluating chemoimmunotherapy options for mCRPC.

Prostate cancer is the second most common cancer among men globally, with metastatic disease representing a significant cause of morbidity and mortality. While androgen deprivation therapy (ADT) forms the cornerstone of treatment, most patients eventually progress to castration-resistant prostate cancer (CRPC). For mCRPC, treatment options include second-generation anti-androgens, chemotherapy (e.g., docetaxel, cabazitaxel), radium-223, and PARP inhibitors for specific genetic subsets. Despite these advancements, the median overall survival for mCRPC patients remains limited, underscoring the need for novel therapeutic strategies. Immunotherapy, particularly immune checkpoint inhibitors (ICIs), has revolutionised the treatment landscape for many cancers, yet its efficacy as monotherapy in prostate cancer has been modest, largely attributed to the immunosuppressive tumour microenvironment and low mutational burden in many prostate tumours. This has led to investigations into combination strategies, such as chemoimmunotherapy, to potentially enhance immune responses and improve clinical outcomes. The rationale for combining chemotherapy with immunotherapy is multifaceted: chemotherapy can induce immunogenic cell death, release tumour antigens, and deplete immunosuppressive cells, thereby potentially sensitising tumours to ICI therapy. This approach aims to overcome the inherent resistance of prostate cancer to immunotherapy alone, by creating a more favourable immune environment within the tumour. The current study explored such a combination in a cohort of mCRPC patients, aiming to identify if a specific regimen could extend progression-free survival.

## The trial

The study was a multicentre, randomised, open-label, Phase III trial that enrolled 1,200 patients with metastatic castration-resistant prostate cancer. Patients were randomised 1:1 to receive either standard chemotherapy alone or chemotherapy in combination with an immune checkpoint inhibitor. Eligibility criteria included histologically confirmed prostate adenocarcinoma, evidence of metastatic disease, castration-resistant status (testosterone 90% power to detect a hazard ratio (HR) of 0.75 for PFS, assuming a median PFS of 6.0 months in the control arm.

The median age of patients was 69 years (range: 48-89). Approximately 70% of patients had visceral metastases, and 30% had bone-only disease. Prior docetaxel chemotherapy for metastatic hormone-sensitive prostate cancer was reported in 45% of patients. The median follow-up duration for PFS was 18.5 months. The combination arm demonstrated a statistically significant improvement in PFS compared to chemotherapy alone, with a median PFS of 8.5 months versus 6.1 months (HR: 0.72; 95% CI: 0.61-0.85; P=0.0001). This translates to a 28% reduction in the risk of progression or death. The objective response rate was also higher in the combination arm at 35% compared to 22% in the control arm (P0.001). While overall survival data were not mature at the time of this analysis, an early trend favoured the combination arm (HR: 0.85; 95% CI: 0.70-1.03; P=0.09). Subgroup analysis revealed that patients with a high tumour mutational burden (TMB-H) or specific homologous recombination repair (HRR) gene alterations derived a greater benefit from the chemoimmunotherapy regimen, with HRs for PFS in these subgroups being 0.55 (95% CI: 0.40-0.76) and 0.62 (95% CI: 0.48-0.80), respectively. Conversely, patients with low TMB or no HRR alterations showed a more modest, non-statistically significant benefit. The safety profile of the combination therapy was consistent with the known toxicities of each agent. Grade 3 or higher adverse events occurred in 65% of patients in the combination arm versus 52% in the control arm. Immune-related adverse events (irAEs) of Grade 3 or higher were observed in 12% of patients receiving chemoimmunotherapy, with colitis and pneumonitis being the most common. These were generally manageable with corticosteroids and supportive care, leading to treatment discontinuation in 8% of patients in the combination arm due to irAEs.

The observed PFS benefit, particularly in molecularly defined subgroups, suggests that patient selection is critical for optimising outcomes with this chemoimmunotherapy approach. The study's findings provide a basis for further investigation into predictive biomarkers that can identify patients most likely to respond. While the overall survival data are still pending, the significant improvement in PFS and ORR represents a meaningful advance for a subset of mCRPC patients. Limitations of the study include its open-label design, which could introduce bias, although objective endpoints like PFS are less susceptible. The relatively short follow-up for overall survival is also a limitation, as OS remains the gold standard for oncology trials. Future research should focus on validating these findings in independent cohorts, further characterising the optimal patient population, and exploring the long-term safety and efficacy of this regimen.

For a comprehensive overview of oncology principles and practice, including relevant treatments for prostate cancer, the Oxford Handbook of Oncology offers essential reading.

> **CLINICAL IMPLICATIONS**
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> The data presented, demonstrating a statistically significant improvement in progression-free survival with a chemoimmunotherapy regimen in mCRPC, warrants careful consideration by clinicians. While the overall hazard ratio of 0.72 for PFS is compelling, the more pronounced benefit observed in patients with high

tumour mutational burden or homologous recombination repair gene alterations underscores the increasing importance of molecular profiling in guiding treatment decisions for prostate cancer. This is not a blanket recommendation for all mCRPC patients; rather, it suggests a targeted approach that aligns with the principles of precision oncology. The incremental increase in Grade 3 or higher adverse events, particularly immune-related events, necessitates vigilance and experience in managing these toxicities, which may not be universally available in all clinical settings.

From an industry perspective, these results will undoubtedly fuel further investment into biomarker-driven trials for prostate cancer. The identification of specific subgroups that benefit most from immunotherapy combinations provides a clearer path for drug development and regulatory approval, moving away from broad, unselected patient populations where immunotherapy has historically underperformed in prostate cancer. Companies developing diagnostic assays for TMB and HRR gene alterations will also see increased relevance. However, the cost-effectiveness of such combination therapies, especially when applied to a smaller, molecularly defined patient population, will be a critical factor for healthcare systems globally.

For patients, these findings offer a potential new avenue for extending disease control, particularly for those whose tumours exhibit specific molecular characteristics. It reinforces the need for comprehensive genomic testing at diagnosis or progression to mCRPC, as these results directly impact treatment selection. Patients should engage in detailed discussions with their oncologists regarding the benefits, risks, and the necessity of molecular profiling to determine if this chemoimmunotherapy regimen is appropriate for their individual disease profile. The prospect of improved PFS, even with increased toxicity, may be a welcome trade-off for patients facing a disease with limited treatment options.

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