Apalutamide + ADT: Is intensified blockade the answer for prostate cancer?

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For men diagnosed with high-risk localized prostate cancer, the specter of recurrence and distant metastasis looms large, even after definitive surgery. The standard approach of androgen deprivation therapy (ADT) around the time of prostatectomy has offered some benefit, but a significant proportion of these patients still progress. The field has long sought an intensified regimen to improve these outcomes.

New data from the phase III PROTEUS trial, published in the New England Journal of Medicine, now provides a clear answer: adding apalutamide to perioperative ADT significantly reduces the risk of metastasis and death.1

KEY TAKEAWAYS

- The Pivot: Apalutamide, an androgen receptor inhibitor, combined with ADT, significantly improved metastasis-free survival compared to ADT alone in high-risk localized prostate cancer.
- The Data: At 5 years, 78.2% of patients on apalutamide plus ADT were metastasis-free and alive, compared with 73.5% on ADT alone, an absolute difference of 4.7%.1
- The Action: Clinicians should consider this intensified perioperative regimen for eligible patients with high-risk localized prostate cancer to reduce long-term metastatic risk.

High-risk localized prostate cancer presents a formidable challenge. Despite radical prostatectomy, a substantial number of patients will experience biochemical recurrence, and a subset will develop distant metastases, which is often a precursor to mortality. Androgen deprivation therapy, or ADT, has been a cornerstone of prostate cancer management for decades, targeting the androgen receptor pathway that fuels prostate cancer growth. But ADT alone has its limitations, particularly in aggressive disease where resistance mechanisms can emerge. The question for clinicians has been whether intensifying this androgen blockade could translate into better long-term outcomes for patients facing this high-risk scenario.1

The PROTEUS trial, a multinational, randomized, double-blind, placebo-controlled phase III study, sought to answer this by evaluating the addition of apalutamide to perioperative ADT. Apalutamide is a second-generation androgen receptor inhibitor that binds directly to the androgen receptor, preventing androgen binding, inhibiting androgen receptor nuclear translocation, and impeding DNA binding. This mechanism of action provides a more complete blockade of the androgen receptor pathway than ADT alone. The trial enrolled 1,847 men with high-risk localized or locally advanced prostate cancer, defined by factors such as Gleason score 8 or higher, clinical stage T3-T4, or prostate-specific antigen (PSA) levels greater than 20 ng/mL.1

Designing the intensified blockade

Patients were randomized 1:1 to receive either apalutamide 240 mg daily plus ADT or placebo plus ADT. The ADT regimen consisted of a gonadotropin-releasing hormone (GnRH) agonist or antagonist, administered for 6 months both before and after radical prostatectomy. This perioperative approach aimed to reduce tumor burden preoperatively, potentially making surgery more effective, and to suppress residual microscopic disease postoperatively. The primary endpoint was metastasis-free survival (MFS), defined as the time from randomization to the first documented evidence of distant metastasis or death from any cause. Secondary endpoints included overall survival (OS), biochemical recurrence-free survival (BRFS), and safety.1

The trial's design was robust, including a diverse patient population across numerous international sites, which strengthens the generalizability of the results. Patients were stratified by Gleason score, clinical T stage, and nodal status, ensuring balance between the treatment arms for these critical prognostic factors. The median follow-up for the study was 44.1 months, providing sufficient time to observe meaningful differences in long-term endpoints like MFS.1

The numbers: a clear benefit

Apalutamide plus ADT significantly improved metastasis-free survival compared with ADT alone. At 5 years, the MFS rate was 78.2% in the apalutamide group versus 73.5% in the placebo group. This represents an absolute difference of 4.7% in favor of the intensified regimen. The hazard ratio for MFS was 0.66 (95% CI, 0.51-0.86; P=.002), indicating a 34% reduction in the risk of metastasis or death. This P-value, well below the conventional threshold, confirms the statistical significance of the observed benefit.1,2

The benefit extended to secondary endpoints as well. Biochemical recurrence-free survival also favored the apalutamide arm, although specific hazard ratios and P-values for this endpoint were not detailed in the abstracts. The trend for overall survival, while not yet mature, also pointed towards a benefit with apalutamide, though the trial was not powered to detect a statistically significant difference in OS at this interim analysis. These consistent signals across multiple endpoints bolster the confidence in the primary MFS finding.1,3

Safety data showed that the addition of apalutamide increased the incidence of certain adverse events, consistent with its known safety profile. Grade 3 or 4 adverse events occurred in 42.1% of patients in the apalutamide group compared with 36.5% in the placebo group. The most common adverse events leading to discontinuation of apalutamide were rash and fatigue. Hypertension and falls were also more frequent in the apalutamide arm, reflecting the systemic effects of potent androgen receptor inhibition. These side effects are generally manageable, but clinicians must counsel patients thoroughly on the potential for increased toxicity.1

Interpreting the clinical impact

The 4.7% absolute improvement in 5-year metastasis-free survival is clinically meaningful for a population at high risk of progression. For every 100 patients treated with apalutamide plus ADT, nearly 5 more will avoid metastasis or death at 5 years compared to those receiving ADT alone. This translates to a number needed to treat (NNT) of approximately 21 to prevent one metastatic event or death over 5 years. This NNT is within a range often considered acceptable for oncology interventions, particularly in a curative-intent setting.1

The duration of treatment, 6 months preoperatively and 6 months postoperatively, is also a practical consideration. This finite treatment period, rather than indefinite therapy, may improve patient adherence and reduce the cumulative burden of side effects. The perioperative timing is key, aiming to hit the cancer hard when it is most vulnerable, before and

immediately after surgical removal of the primary tumor. This strategy aligns with principles of neoadjuvant and adjuvant therapy in other solid tumors.1

Still, the trial was not powered to detect differences in specific subgroups, and that gap matters. While the overall benefit is clear, whether certain high-risk features (e.g., specific genomic alterations, very high PSA levels, extensive nodal involvement) predict a greater or lesser response to apalutamide remains an area for further investigation. The current data provides a broad brushstroke, but personalized treatment decisions may require more granular evidence. For clinicians managing these complex cases, having a comprehensive reference like the Oxford Handbook of Oncology can be invaluable for navigating treatment options and understanding the nuances of cancer management.1

The open-label design of the surgical intervention itself is the obvious caveat. While the drug and placebo were blinded, the fact that patients underwent surgery is not. This is an inherent limitation of surgical trials, but it does not diminish the robust blinding of the investigational agent. The primary endpoint, MFS, is also a hard endpoint, less susceptible to subjective bias than quality of life measures, though those were also collected. The trial's reliance on imaging for metastasis detection, while standard, means that microscopic metastases not visible on conventional scans would not be captured, potentially underestimating the true burden of disease.1

The long-term safety profile of extended androgen receptor inhibition in this perioperative setting will also require continued monitoring. While the 5-year data is encouraging, prostate cancer is often a disease of older men, and the cumulative effects of ADT and apalutamide on bone health, cardiovascular risk, and cognitive function over decades are important considerations. The trial's follow-up will continue to track these outcomes, providing important insights into the enduring impact of this intensified regimen.1

CLINICAL IMPLICATIONS

The PROTEUS trial delivers a clear message: apalutamide plus ADT is superior to ADT alone for high-risk localized prostate cancer. This 4.7% absolute improvement in 5-year metastasis-free survival is not trivial; it represents a tangible benefit for patients who face a significant risk of progression. This data will undoubtedly prompt a re-evaluation of current treatment algorithms for this patient population.

For urologists and oncologists, the decision to intensify therapy with apalutamide now has strong evidence behind it. The increased toxicity, while present, appears manageable and aligns with the known profile of apalutamide. The finite 6-month perioperative duration also makes this regimen more appealing than indefinite treatment.

The next step for the field is to integrate these findings into clinical guidelines. Expect to see apalutamide, in combination with ADT, become a new standard of care for carefully selected high-risk localized prostate cancer patients. Further research will likely focus on identifying specific biomarkers to predict which patients will derive the greatest benefit from this intensified approach.

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