# Proteus Trial

*The phase 3 trial met both dual primary endpoints (MFS and pCR/MRD), showing a significant improvement in both short- and long-term outcomes.*

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**Key Points:**

- The phase 3 PROTEUS trial tested whether adding apalutamide to androgen deprivation therapy (ADT) before and after radical prostatectomy improved outcomes in men with high-risk prostate cancer.
- The study met both dual primary endpoints of pathologic complete response (pCR)/minimal residual disease (MRD) and metastasis-free survival (MFS), marking a long-awaited therapeutic advance in this setting.
- Apalutamide plus ADT demonstrated a manageable safety profile, with infrequent dose reductions or interruptions and no unexpected signals.

After years of failed attempts to establish a benefit with perioperative systemic therapy in tandem with radical prostatectomy in high-risk localized prostate cancer, the phase 3 PROTEUS trial (NCT03767244) finally delivers. The results show that adding apalutamide to ADT before and after surgery significantly improves both short- and long-term outcomes, enhancing curative success over placebo plus ADT (LBA1).

Administration of 6 cycles of neoadjuvant apalutamide plus ADT conferred an increase of approximately 9-fold in the likelihood of pCR/MRD compared with ADT alone (8.9% vs 1.0%; odds ratio 10.17, 95% CI [5.27, 19.64]; $P < .0001$). Similarly, a favorable residual cancer burden at prostatectomy, defined as ≤ ypT2, N0 ≤ 0.25 $cm^3$, was identified in 30.6% of patients in the apalutamide plus ADT arm versus 11.7% in the placebo plus ADT arm.

Neoadjuvant treatment, combined with an additional 6 cycles of apalutamide and ADT after radical prostatectomy, resulted in a 20% decrease in the relative risk of metastasis or death (HR 0.80, 95% CI [0.67, 0.96]; $P = .0169$). Median MFS was not reached in either arm, but the 5-year MFS rate was 78.2% in the apalutamide plus ADT arm versus 73.5% in the placebo plus ADT arm (Figure).

**Figure.** PROTEUS Primary Endpoint: MFS Results **Abbreviations:** ADT, androgen deprivation therapy; APA, apalutamide; BICR, blinded independent central review; MFS, metastasis-free survival; PBO, placebo; PSMA, prostate-specific membrane antigen; RP, radical prostatectomy. [a]HR is from stratified proportional hazards model; HR < 1 favors APA + ADT. [b]*P* value is from a log-rank test stratified by Gleason score (7 or ≥ 8), nodal status (N0 or N1), and geographic region (North America, Europe, or rest of the world). View larger.

"These results have the potential to be practice changing and support perioperative apalutamide plus ADT as a new standard of care for patients with high-risk localized prostate cancer who are candidates for radical prostatectomy," remarked Lead Investigator Mary-Ellen Taplin, MD, FASCO,

of the Dana-Farber Cancer Institute, who presented the findings at the Plenary Session during the 2026 ASCO Annual Meeting.

**“I will certainly be incorporating this intensified hormonal therapy regimen into my practice for men with more aggressive high-risk localized prostate cancer features,” commented Discussant Declan Murphy, MB BCh, of the Peter MacCallum Cancer Centre in Melbourne, Australia**. “I believe that the benefits reported in PROTEUS today, not just in the primary endpoints but also in the delayed and reduced requirement for subsequent therapy, will be very attractive to my patients and will be considered worthwhile.”

## PROTEUS Rationale and Design Features

Depending on their disease, up to 50% of patients with high-risk localized prostate cancer experience disease relapse within 5 years of radical prostatectomy, underscoring the limitations of surgery alone despite decades of refinement.[1-5] Although multiple attempts over the years to augment prostatectomy with neoadjuvant or perioperative systemic therapy pointed toward pathologic and/or biochemical improvements, none established clear clinical benefits in high-risk disease, such as reducing metastatic relapse rates.

Apalutamide is an oral androgen receptor pathway inhibitor approved by the U.S. Food and Drug Administration for the treatment of nonmetastatic castration-resistant prostate cancer and metastatic castration-sensitive prostate cancer.[6] PROTEUS was designed to evaluate whether intensifying treatment with 12 cycles of perioperative apalutamide and ADT, split equally before and after radical prostatectomy, could improve outcomes in patients with high-risk localized prostate cancer.

The 2,109 patients enrolled in the trial were stratified by Gleason score, nodal status, and geographic region before being randomly assigned to apalutamide or placebo, each in combination with ADT.

“PROTEUS is the largest phase 3 placebo-controlled therapeutic trial ever carried out in this disease setting. Furthermore, it accrued patients from 18 countries, making the PROTEUS population culturally and racially diverse,” Dr. Taplin remarked.

By pairing pCR/MRD with MFS as dual primary endpoints, the trial was designed to assess both early tumor response at surgery and whether that response translated into meaningful long-term benefit. Notably, the trial integrated prostate-specific membrane antigen–PET with conventional imaging for MFS assessment, consistent with evolving clinical guidance, and prospectively collected prostate tissue for biomarker analysis.

## Secondary Endpoint Results and Safety

The addition of apalutamide to ADT resulted in a significant 18.7-month increase in median event-free survival, improving from 38.4 months with ADT alone to 57.1 months with the combination (HR 0.71, 95% CI [0.63, 0.80]; $P < .0001$). This improvement was largely driven by lower rates of biochemical failure (77% vs 80%) and locoregional recurrence (9% vs 11%) with inclusion of apalutamide.

Apalutamide plus ADT also significantly delayed the development of distant metastasis, with 83% of patients remaining metastasis free at 5 years compared with 76% in the ADT-alone arm (HR 0.68, 95% CI [0.55, 0.83]; *P* = .0002). Similarly, a significantly higher proportion of men had no evidence of disease at 4 years (21.9% vs 18.3%; *P* = .04).

Administering 1 year of perioperative apalutamide and ADT spared patients from subsequent therapy for a median of 6.2 years, compared with 3.5 years with ADT alone—an improvement of 2.7 years (HR 0.65, 95% CI [0.57, 0.73]; *P* < .0001).

“All of this adds up to a much better patient journey,” Dr. Murphy remarked.

“The safety signals with apalutamide plus ADT were consistent with the known safety profile of this combination,” according to Dr. Taplin (Table). Among adverse events of special interest, skin rash occurred most frequently with apalutamide and at a notably higher rate than with placebo (33.0% vs 15.3%).

**Table.** PROTEUS: Frequency of TEAEs **Abbreviations:** ADT, androgen deprivation therapy; AE, adverse event; APA, apalutamide; PBO, placebo; RP, radical prostatectomy; TEAE, treatment-emergent AE. [a]AEs leading to treatment interruption, dose reduction, or discontinuation are based on AE action taken. [b]An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study drug (apalutamide or placebo), ADT, or RP. [c]Includes grade 5 events. [d]AEs leading to death are based on AE outcome of fatal. View larger.

# Future Directions

“PROTEUS is a landmark trial and will continue to deliver very informative data over the coming months and years as we see more data,” Dr. Murphy commented. “Importantly, we have not seen any patient-reported outcome measures regarding quality of life, which is a key consideration for the management of high-risk localized prostate cancer, and we look forward to seeing these data.”

Indeed, forthcoming PROTEUS updates will focus on patient-reported outcomes, biomarker analyses, and correlation of major pathologic response with MFS, as well as a substudy that compares apalutamide, ADT, and surgery versus surgery alone. “We also plan several post hoc analyses of the PROTEUS data to understand the implications for routine clinical practice,” Dr. Taplin said.

**—Kara Nyberg, PhD**

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