

Exposure-response relationships of the efficacy and safety of apalutamide in non-metastatic castration-resistant prostate cancer subjects



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INTRODUCTION:

Apalutamide (APA; ERLEADA®), an orally administered selective androgen receptor inhibitor,¹ is approved for the treatment of men with non-metastatic castration-resistant prostate cancer (nmCRPC) based on the pivotal phase 3 clinical study SPARTAN, which studied apalutamide plus androgen deprivation therapy (ADT).²

OBJECTIVE:

To understand the relationship between exposure to APA and its active metabolite N-desmethyl-apalutamide (N-APA) and selected clinical efficacy and safety endpoints to support APA dosing recommendations in men with high risk nmCRPC.

METHODS:

Data from 1207 subjects (806 APA 240 mg and 401 placebo) in the SPARTAN study were included in the exposure-response (ER) analysis. Using a population pharmacokinetics (popPK) model developed in NONMEM® software,³ exposures of APA and N-APA were quantified as the area under the concentration-time curve at steady state (AUC_{0-24h,ss}) at the average daily dose received up to the day of metastatic progression or adverse event.

Efficacy

Univariate and multivariate Cox regression models evaluated the relationships between APA and N-APA AUC_{0-24h,ss} and the primary outcome of the study, metastasis free survival (MFS) and were adjusted by pre-specified stratification factors. In the multivariate Cox regression analysis, the impact of APA and N-APA exposure on MFS, was assessed by the hazard ratio (HR) and its 95% confidence interval (CI).

Safety

Univariate and multivariate logistic regression models assessed the relationship between APA and N-APA AUC_{0-24h,ss} and common treatment emergent adverse events (TEAEs): fatigue, fall, skin rash, weight decrease, and arthralgia. The corresponding odds ratio (OR), 95% CI, χ^2 and p-values were calculated.

RESULTS

Figure 1: Kaplan Meier plot for MFS as a function of placebo and the lowest exposure quartile (Q1) to highest exposure quartile (Q4) of APA and N-APA plasma steady-state AUC_{0-24h,ss}

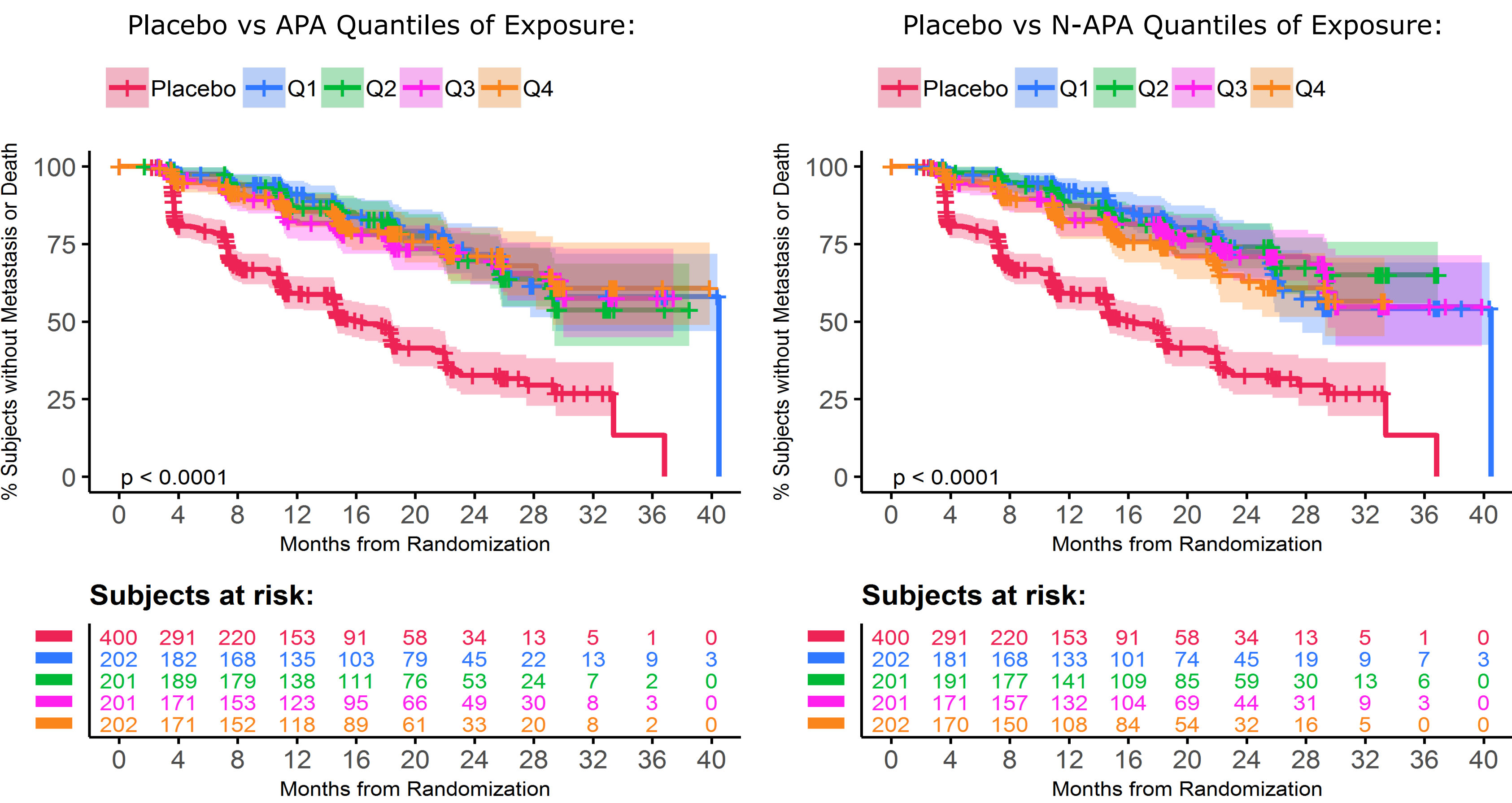
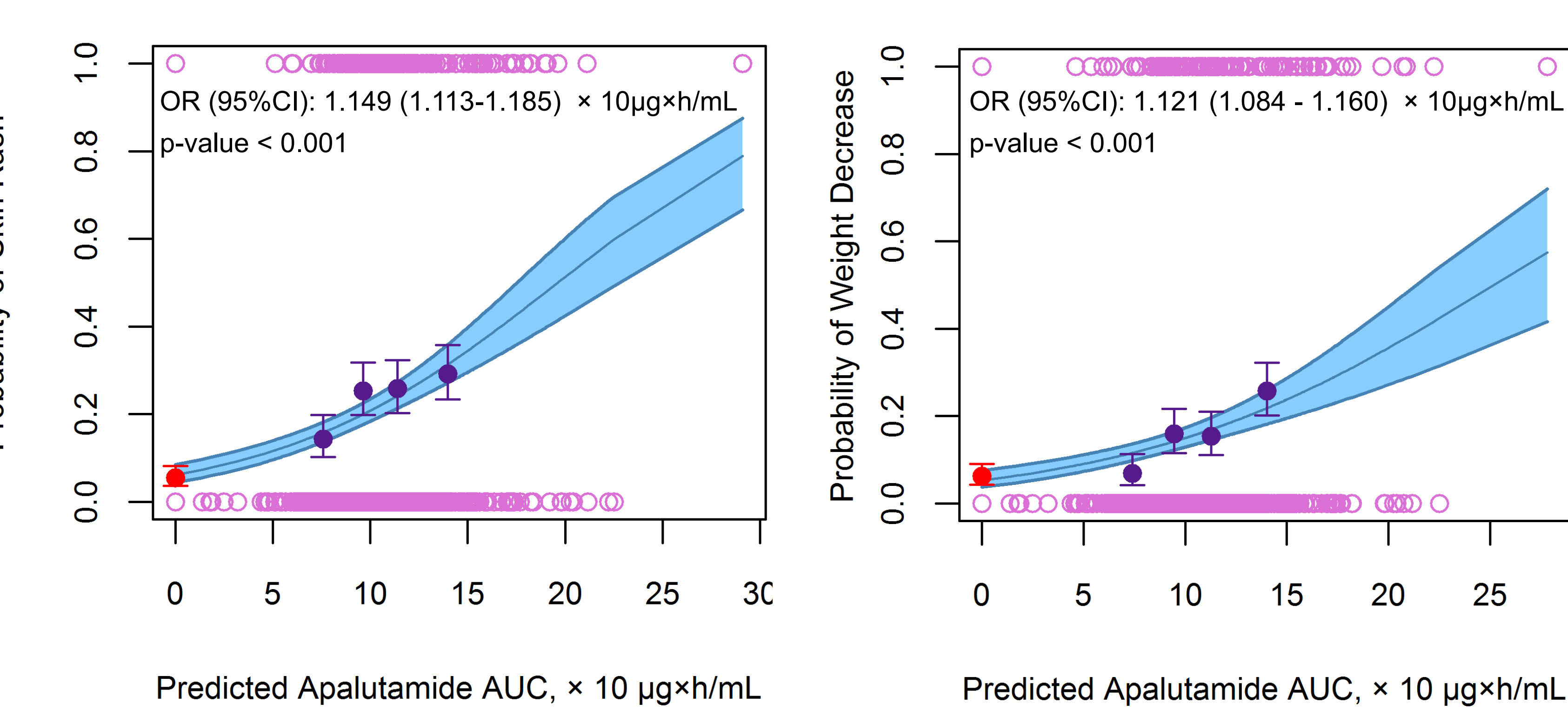


Figure 2: Logistic regression representing the probability of experiencing skin rash and weight decrease as function of APA steady-state AUC_{0-24h,ss}



Efficacy: The uni- (Fig 1) and multivariate (Table 1) Cox regression analyses showed no statistically significant relationship between MFS, APA, and N-APA when categorized by quartiles of exposure or when used as a continuous variable suggesting that differences in APA and N-APA exposure within the range observed in SPARTAN are not associated with clinically relevant differences in MFS. On the other hand, PSADT, loco-regional disease and ECOG were statistically associated with MFS.

Table 1: Results of the multivariate Cox regression analysis for MFS for the SPARTAN population

Multivariate Analysis	HR 95%CI	P-value
Treatment (Apalutamide vs Placebo)	0.205 (0.097–0.435)	<0.001
APA AUC _{0-24h} (µg×h/mL)	0.999 (0.990–1.008)	0.810
N-APA AUC _{0-24h} (µg×h/mL)	1.003 (0.995–1.011)	0.495
PSADT (≤ 6 months vs. > 6 months)	1.635 (1.278–2.091)	<0.001
Bone sparing agent use (yes vs. no)	0.829 (0.582–1.180)	0.297
Presence of loco regional disease (N1 vs. N0)	1.516 (1.162–1.977)	0.002
Age (years)	0.992 (0.978–1.005)	0.219
ECOG (Grade 1 vs. Grade 0)	1.300 (1.022–1.654)	0.033

Safety: The uni- (Fig 2) and multivariate (Table 2) logistic regression analyses demonstrated that within the exposure range observed in men treated with APA, the exposure-TEAEs relationship was statistically significant for skin rash and weight decrease. Using Li's method, APA exposure explained 57% and 38.8% of the effect on rash and weight decrease, respectively.⁴

Table 2: Results of the multivariate logistic regression analysis for skin rash and weight decrease for the SPARTAN population

Multivariate Analysis	OR 95%CI	P-value
Skin Rash:		
Treatment (Apalutamide vs Placebo)	1.484 (0.703–3.148)	0.301
APA AUC _{0-24h} (µg×h/mL)	1.123 (1.067–1.185)	<0.001
Weight Decrease:		
Treatment (Apalutamide vs Placebo)	0.540 (0.239–1.209)	0.136
APA AUC _{0-24h} (µg×h/mL)	1.162 (1.097–1.233)	<0.001

CONCLUSIONS

The ER analyses demonstrated that differences in APA and N-APA exposure with a starting dose of 240-mg daily are not expected to be associated with clinically relevant differences in MFS in men with nmCRPC. The exposure-safety analysis supports the dose reductions to 180 or 120 mg/day in subjects who experienced TEAEs, such as skin rash.

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