# Apalutamide for Metastatic Castration-Sensitive Prostate Cancer in TITAN: Prognostic Importance of Prostate-Specific Antigen Responses

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# Background: TITAN Phase 3 Study

- Apalutamide is an oral nonsteroidal antiandrogen agent that binds to the androgen receptor and prevents nuclear translocation, DNA binding, and androgen receptor–mediated transcription[1]
- The phase 3 TITAN study showed that apalutamide plus androgen deprivation therapy (ADT) significantly improves overall survival (OS), radiographic progression-free survival (rPFS), and time to prostate-specific antigen (PSA) progression in a broad population of patients with metastatic castration-sensitive prostate cancer (mCSPC)[2]
- This post hoc analysis of the TITAN study data evaluated PSA declines and associations with clinical outcomes



1. Clegg NJ, et al. *Cancer Res*. 2012;72:1494-1503; 2. Chi KN, et al. *N Engl J Med*. 2019;381:13-24.

# TITAN Study Design

**Broad patient population**

**Key eligibility criteria**
- Castration sensitive
- Distant metastatic disease by ≥ 1 lesion on bone scan
- ECOG PS 0 or 1

**On-study requirement**
- Continuous ADT

**Permitted**
- Prior docetaxel
- ADT ≤ 6 mo for mCSPC or ≤ 3 yr for local disease
- Local treatment completed ≥ 1 yr prior

**Stratifications**
- Gleason score at diagnosis (≤ 7 vs ≥ 8)
- Region (NA and EU vs all other countries)
- Prior docetaxel (yes vs no)

**N = 1052**

**Dec 2015 – Jul 2017**

1:1 RANDOMIZATION

**Apalutamide 240 mg daily + ADT (n = 525)**

**Placebo + ADT (n = 527)**

**Dual primary end points**
- **OS**
- **rPFS**

**Secondary end points**
- Time to cytotoxic chemotherapy
- Time to pain progression
- Time to chronic opioid use
- Time to skeletal-related event

**Exploratory end points**
- Time to PSA progression[a]
- Second progression-free survival (PFS2)
- Time to symptomatic progression

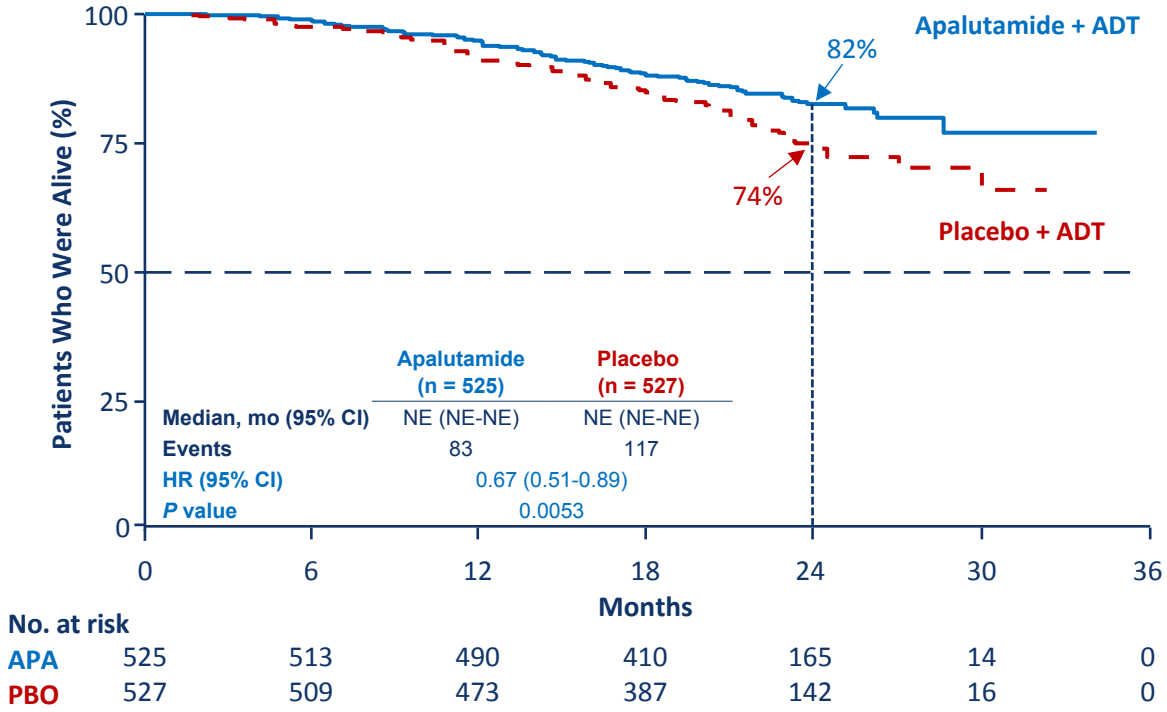
[a]Based on Prostate Cancer Clinical Trials Working Group (PCWG2) criteria.

ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; NA, North America.

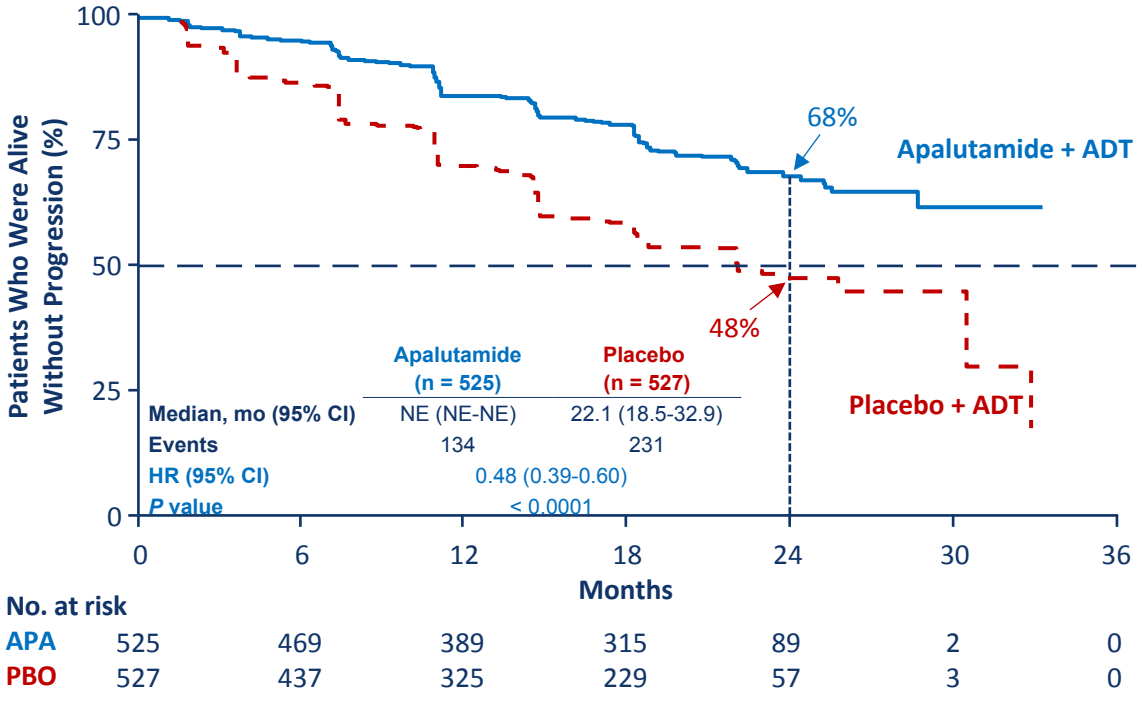
Chi KN, et al. Presented at: American Society of Clinical Oncology. 2019; Abstract 5006

# Rates of Both rPFS and OS Were Significantly Improved With Apalutamide Versus Placebo[1]

## Apalutamide Significantly Reduced the Risk of Death by 33%




## Apalutamide Significantly Reduced the Risk of Radiographic Progression or Death by 52%




APA, apalutamide; CI, confidence interval; HR, hazard ratio; NE, not estimable; PBO, placebo.

1. Chi KN, et al. *N Engl J Med*. 2019;381:13-24

# Methods: Correlation of PSA Response With Clinical Outcomes in TITAN

- 1052 patients with mCSPC receiving ADT were randomized 1:1 to apalutamide (240 mg/d, n = 525) or placebo (n = 527); median follow-up was 22.7 months[1]
- Depth of PSA response was evaluated by categorizing patients with PSA decline to ≤ 0.2 ng/mL or decline by < 50%, ≥ 50%-90%, or ≥ 90% from baseline
- Time to castration resistance (CRPC) was the time to PSA progression (PCWG2 criteria),[2] skeletal-related event, or radiographic progression, whichever came first
- OS was defined as the time from randomization to date of death from any cause
- rPFS was defined as the time from randomization to first documentation of radiographic progressive disease or death, whichever came first
- Trial registration: NCT02489318

PCWG2, Prostate Cancer Working Group 2.

1. Chi KN, et al. *N Engl J Med*. 2019;381:13-24. 2. Scher HI, et al. *J Clin Oncol.* 2008;26:1148-1159.

# The Depth of PSA Response With Apalutamide Was Superior to That With Placebo

| | APA (n = 525) | PBO (n = 527) |
|---|---|---|
| PSA at baseline[a], median (range), ng/mL | 5.97 (0.0-2682.0) | 4.02 (0.0-2228.5) |
| PSA nadir, median (range), ng/mL | 0.03 (0.0-498.4) | 0.92 (0.0-1407.7) |
| Time to PSA nadir, median (range), mo | 5.55 (0.1-25.9) | 3.71 (0.7-25.8) |
| Confirmed PSA response ≥ 50%, n (%) | 473 (90.1)[a] | 274 (52.0) |
| Time to achieve confirmed PSA response ≥ 50%, median (range), mo | 0.95 (0.3-11.1) | 0.95 (0.1-16.6) |
| Confirmed PSA response ≥ 90%, n (%) | 380 (72.4)[a] | 124 (23.5) |
| Time to achieve confirmed PSA response ≥ 90%, median (range), mo | 1.87 (0.3-20.3) | 2.78 (0.1-18.4) |
| Confirmed PSA ≤ 0.2 ng/mL, n (%) | 350 (66.7)[b] | 129 (24.5) |
| Time to achieve confirmed PSA ≤ 0.2 ng/mL, median (range), mo | 1.87 (0.1-20.3) | 0.99 (0.7-20.2) |

[a]At the time of randomization and following at least 2 weeks of ADT
[b]$P < 0.0001$ for APA vs PBO.

# Demographics and Baseline Characteristics

| | Patients with PSA decline to ≤ 0.2 ng/mL | | Patients with PSA declines | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | ≥ 90% | | 50% to < 90% | | < 50% | |
| | APA (n = 350) | PBO (n=129) | APA (n = 380) | PBO (n = 124) | APA (n = 93) | PBO (n = 150) | APA (n = 52) | PBO (n = 253) |
| Age, yr, median (range) | 69.0 (45-94) | 68.0 (45-84) | 69.0 (47-94) | 70.5 (47-90) | 67.0 (45-89) | 67.0 (48-85) | 67.0 (56-87) | 67.0 (43-88) |
| Time from initial diagnosis to randomization, mo, median (range) | 3.93 (0.5-222.9) | 5.72 (1.1-189.5) | 3.09 (0.5-207.8) | 2.37 (0.7-130.4) | 6.54 (1.0-222.9) | 2.97 (0.7-189.5) | 6.64 (1.6-145.9) | 5.22 (1.0-341.4) |
| Gleason score at diagnosis, n (%) | | | | | | | | |
| < 8 | 126 (36.0) | 50 (38.8) | 127 (33.4) | 44 (35.5) | 34 (36.6) | 54 (36.0) | 13 (25.0) | 71 (28.1) |
| ≥ 8 | 224 (64.0) | 79 (61.2) | 253 (66.6) | 80 (64.5) | 59 (63.4) | 96 (64.0) | 39 (75.0) | 182 (71.9) |
| ECOG performance status, n (%) | | | | | | | | |
| 0 | 227 (64.9) | 97 (75.2) | 238 (62.6) | 86 (69.4) | 59 (63.4) | 98 (65.3)[a] | 31 (59.6) | 164 (64.8) |
| 1 | 123 (35.1) | 32 (24.8) | 142 (37.4) | 38 (30.6) | 34 (36.6) | 51 (34.0) | 21 (40.4) | 89 (35.2) |
| Prior docetaxel use, n (%) | 37 (10.6) | 24 (18.6) | 22 (5.8) | 3 (2.4) | 26 (28.0) | 9 (6.0) | 10 (19.2) | 43 (17.0) |
| Extent of disease at study entry, n (%) | | | | | | | | |
| Bone metastases | 350 (100.0) | 129 (100.0) | 380 (100.0) | 124 (100.0) | 93 (100.0) | 150 (100.0) | 52 (100.0) | 253 (100.0) |
| Lymph node metastases | 103 (29.4) | 37 (28.7) | 150 (39.5) | 62 (50.0) | 29 (31.2) | 72 (48.0) | 20 (38.5) | 85 (33.6) |
| Visceral metastases | 31 (8.9) | 10 (7.8) | 40 (10.5) | 14 (11.3) | 5 (5.4) | 21 (14.0) | 11 (21.2) | 37 (14.6) |

[a]One patient treated with PBO had ECOG PS 2 at baseline.

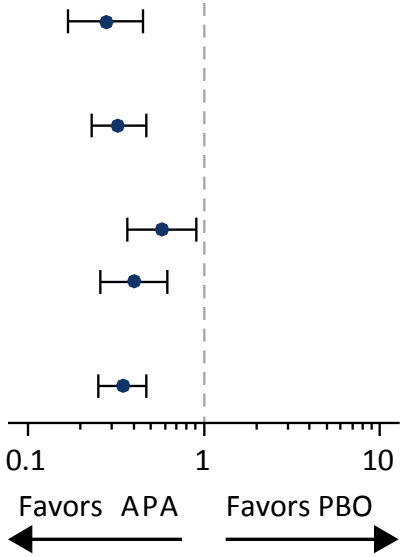
# More Patients in the Apalutamide Group Versus the Placebo Group Achieved PSA Responses Over Time

| PSA Responses Over Time | | | | | | |
|---|---|---|---|---|---|---|
| Decline | 3 months | | 6 months | | 12 months | |
| | APA[a] | PBO | APA[a] | PBO | APA[a] | PBO |
| PSA ≥ 50% ↓ | 89% | 41% | 90% | 49% | 90% | 52% |
| PSA ≥ 90% ↓ | 58% | 13% | 67% | 18% | 71% | 22% |
| PSA ≤ 0.2 ng/mL | 51% | 18% | 61% | 21% | 65% | 23% |

[a]*P* < 0.0001 for APA vs PBO.

# In Patients Treated With Apalutamide, PSA Response Was Associated With Improved rPFS, OS, and Castration Resistance

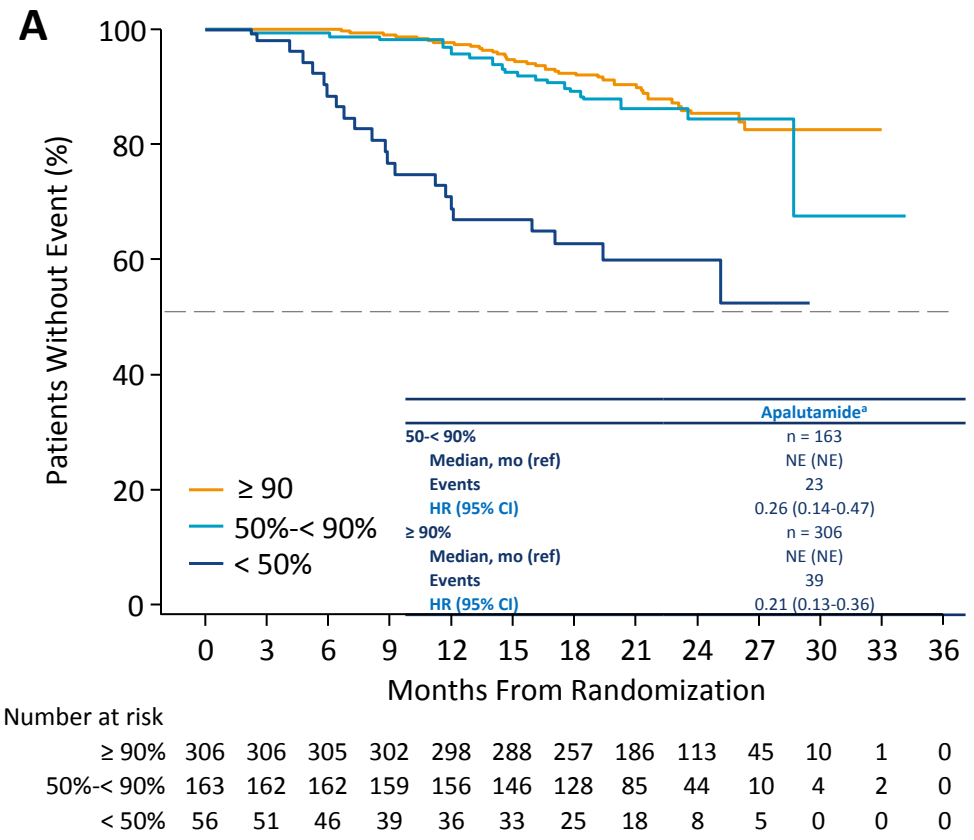
| Variable | Subgroup | Median (months) APA | Median (months) PBO | HR (95% CI) | Events/N APA | Events/N PBO |
|---|---|---|---|---|---|---|
| OS by PSA percent decline | < 50 (ref) | | NE | 1.000 (ref.) | | 21/56 |
| | 50-< 90 | NE | NE | 0.26 (0.14-0.47) | 23/163 | |
| | ≥ 90 | NE | NE | 0.21 (0.13-0.36) | 39/306 | |
| OS – PSA ≤ 0.2 ng/mL | No (ref) | | NE | 1.000 (ref) | | 65/258 |
| | Yes | NE | NE | 0.22 (0.13-0.37) | 18/267 | |
| rPFS by PSA percent decline | < 50 (ref) | | 18.3 | 1.000 (ref) | | 22/56 |
| | 50-< 90 | NE | 18.3 | 0.32 (0.19-0.53) | 40/163 | |
| | ≥ 90 | NE | 18.3 | 0.28 (0.17-0.45) | 72/306 | |
| rPFS – PSA ≤ 0.2 ng/mL | No (ref) | | 25.6 | 1.000 (ref) | | 92/258 |
| | Yes | NE | 25.6 | 0.33 (0.23-0.47) | 42/267 | |
| mCRPC by PSA percent decline | < 50 (ref) | | 18.3 | 1.000 (ref) | | 26/56 |
| | 50-< 90 | NE | 18.3 | 0.58 (0.37-0.91) | 65/163 | |
| | ≥ 90 | NE | 18.3 | 0.40 (0.26-0.62) | 92/306 | |
| mCRPC – PSA ≤ 0.2 ng/mL | No (ref) | | 21.9 | 1.000 (ref) | | 124/258 |
| | Yes | NE | 21.9 | 0.34 (0.25-0.47) | 59/267 | |




CI, confidence interval; HR, hazard ratio

# Patients Who Achieved PSA Response Following 3 Months of Apalutamide Treatment Had Improved OS

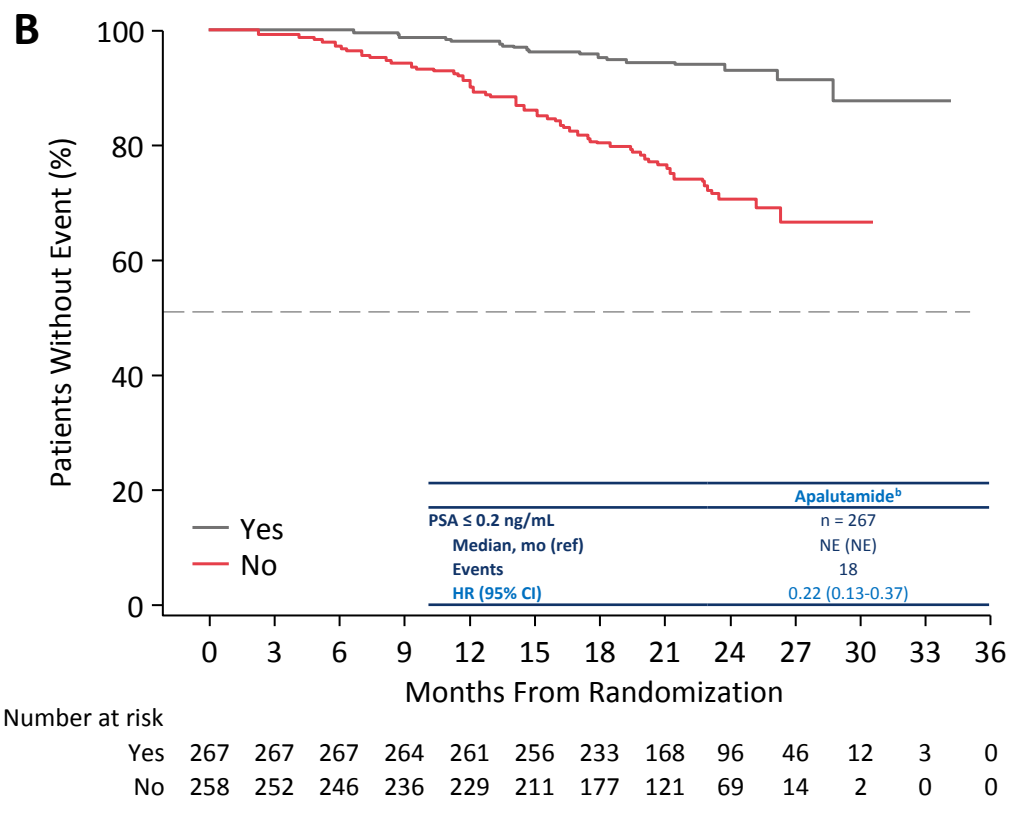
## Patients who achieved reduction of PSA ≥ 90%, PSA 50%-< 90%, and PSA < 50% by 3 months




Number at risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ≥ 90% | 306 | 306 | 305 | 302 | 298 | 288 | 257 | 186 | 113 | 45 | 10 | 1 | 0 |
| 50%-< 90% | 163 | 162 | 162 | 159 | 156 | 146 | 128 | 85 | 44 | 10 | 4 | 2 | 0 |
| < 50% | 56 | 51 | 46 | 39 | 36 | 33 | 25 | 18 | 8 | 5 | 0 | 0 | 0 |

## Patients who achieved PSA ≤ 0.2 ng/mL and those who did not by 3 months



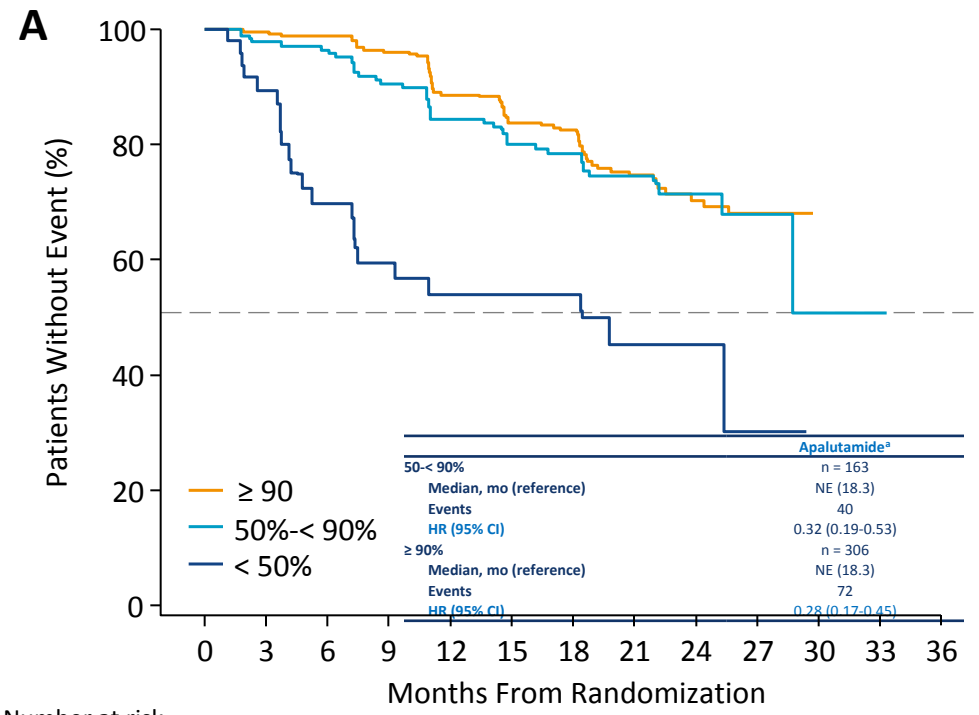

Number at risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Yes | 267 | 267 | 267 | 264 | 261 | 256 | 233 | 168 | 96 | 46 | 12 | 3 | 0 |
| No | 258 | 252 | 246 | 236 | 229 | 211 | 177 | 121 | 69 | 14 | 2 | 0 | 0 |

[a]Reference: PSA decline < 50%; [b]reference: PSA > 0.2 ng/mL.

# Patients Who Achieved PSA Response Following 3 Months of Apalutamide Treatment Had Improved rPFS

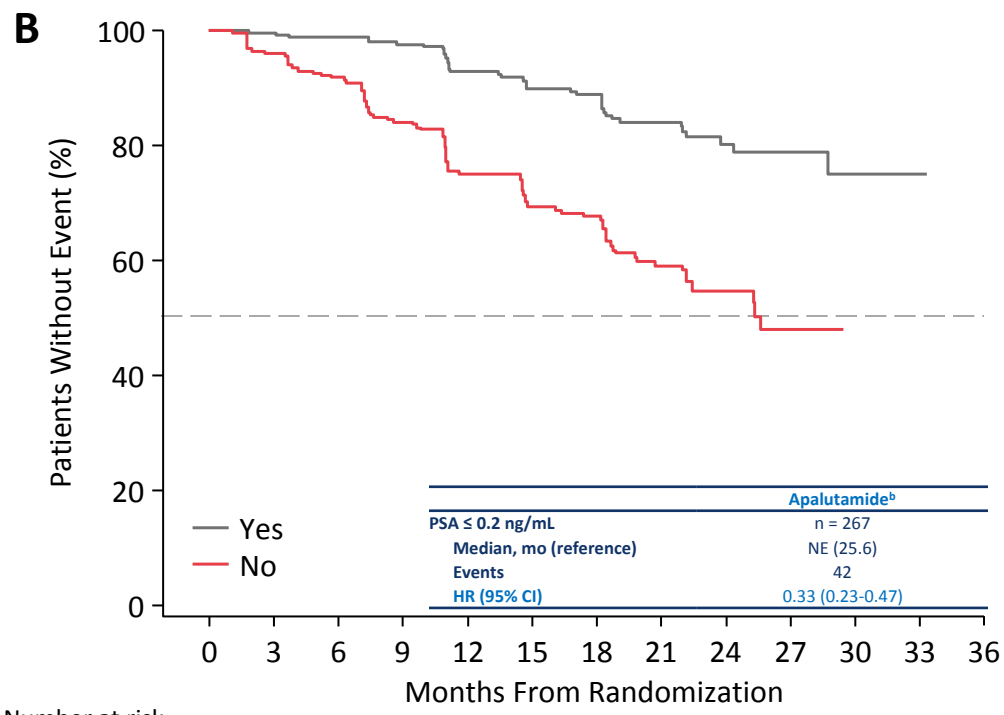
## Patients who achieved reduction of PSA ≥ 90%, PSA 50%-< 90%, and PSA < 50% by 3 months




Number at risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ≥ 90% | 306 | 301 | 291 | 275 | 247 | 207 | 201 | 124 | 65 | 16 | 0 | 0 | 0 |
| 50%-< 90% | 163 | 158 | 151 | 137 | 122 | 102 | 99 | 60 | 21 | 4 | 2 | 1 | 0 |
| < 50% | 56 | 39 | 27 | 22 | 20 | 17 | 15 | 10 | 3 | 1 | 0 | 0 | 0 |

## Patients who achieved PSA ≤ 0.2 ng/mL and those who did not by 3 months



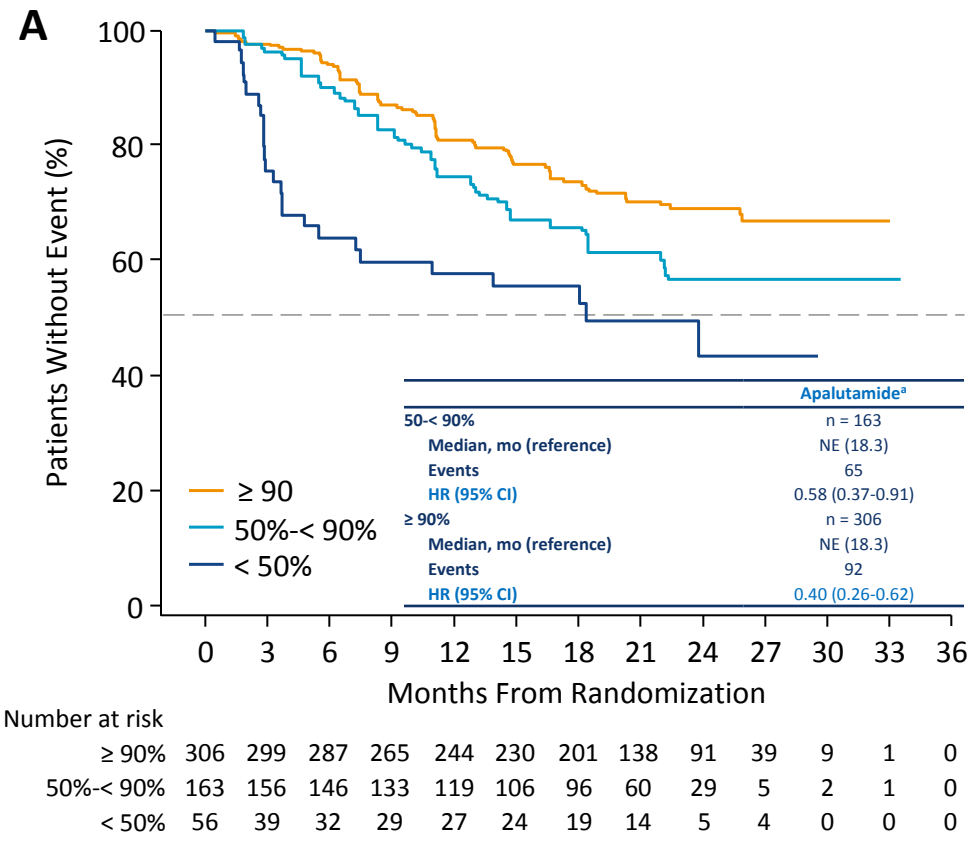

Number at risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Yes | 267 | 262 | 252 | 242 | 224 | 195 | 189 | 117 | 64 | 20 | 2 | 1 | 0 |
| No | 258 | 236 | 217 | 192 | 165 | 131 | 126 | 77 | 25 | 1 | 0 | 0 | 0 |

[a]Reference: PSA decline < 50%; [b]reference: PSA > 0.2 ng/mL.

# Time to Castration Resistance Was Improved in Patients With PSA Response After 3 Months of Apalutamide Treatment

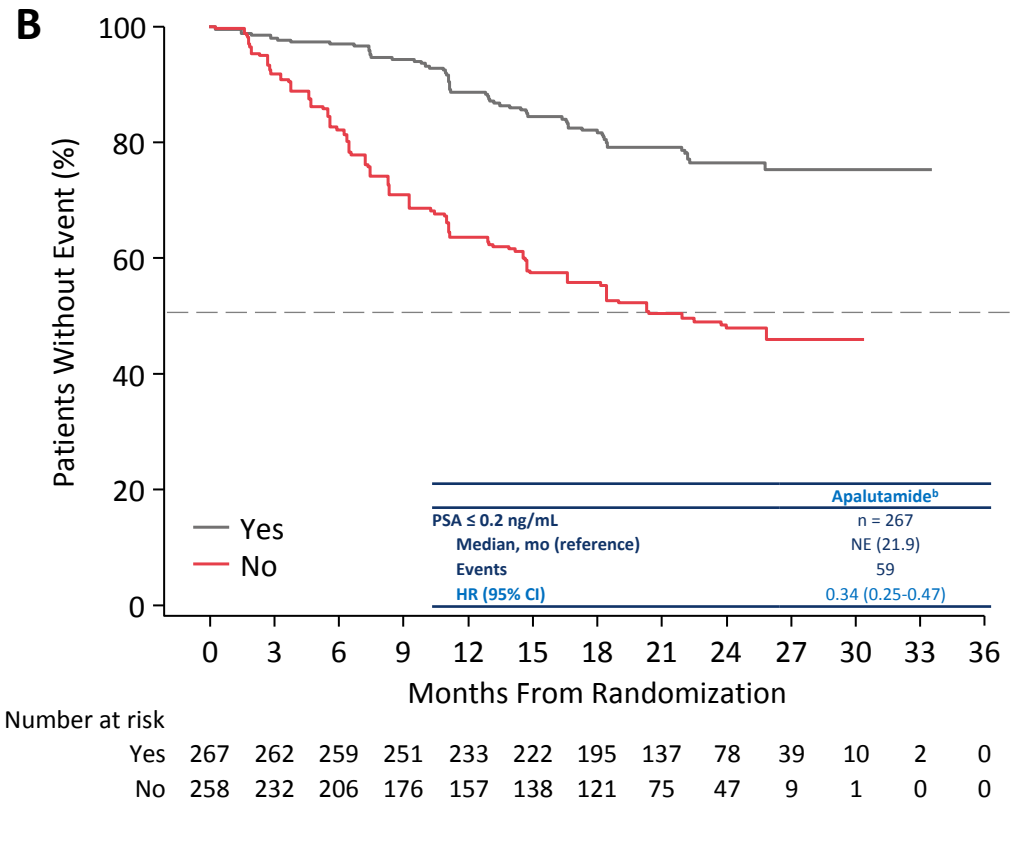
Patients who achieved reduction of PSA ≥ 90%, PSA 50%-< 90%, and PSA < 50% by 3 months




Number at risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ≥ 90% | 306 | 299 | 287 | 265 | 244 | 230 | 201 | 138 | 91 | 39 | 9 | 1 | 0 |
| 50%-< 90% | 163 | 156 | 146 | 133 | 119 | 106 | 96 | 60 | 29 | 5 | 2 | 1 | 0 |
| < 50% | 56 | 39 | 32 | 29 | 27 | 24 | 19 | 14 | 5 | 4 | 0 | 0 | 0 |

Patients who achieved PSA ≤ 0.2 ng/mL and those who did not by 3 months




Number at risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Yes | 267 | 262 | 259 | 251 | 233 | 222 | 195 | 137 | 78 | 39 | 10 | 2 | 0 |
| No | 258 | 232 | 206 | 176 | 157 | 138 | 121 | 75 | 47 | 9 | 1 | 0 | 0 |

[a]Reference: PSA decline < 50%; [b]reference: PSA > 0.2 ng/mL.

# TITAN PSA Response Conclusions

- Treatment with apalutamide plus ADT demonstrated a robust response in serum PSA levels that were sustained over time in patients with mCSPC
- The magnitude of PSA response was significantly improved with the addition of apalutamide to ADT compared with placebo plus ADT
- The magnitude and depth of PSA response was associated with a significant extension/improvement of OS and a significant reduction/delay in radiographic progression, and the development of castration resistance
- Deep and rapid PSA response with apalutamide plus ADT as early as 3 months was associated with significantly improved long-term clinical outcomes indicating prognostic impact

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