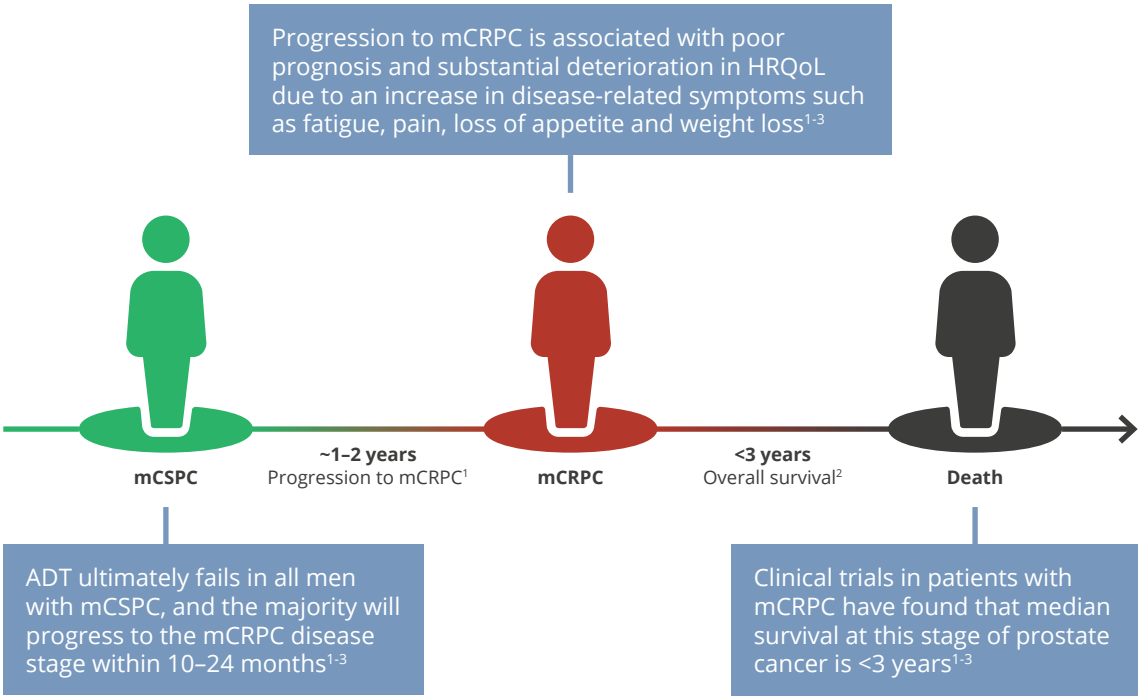
PHYSICIAN VALUE MESSAGES AND KEY SUPPORTING EVIDENCE FOR APALUTAMIDE

UNMET NEED

Once patients progress to mCRPC, prognosis is poor and median survival is <3 years. mCSPC is a critical intervention point and represents the final opportunity to delay progression to mCRPC once metastases have been diagnosed.

In patients with mCSPC, CAB/ADT alone is not enough. It is critical to use a powerful treatment in addition to CAB/ADT to push back progression, symptoms and death.



The effect of CAB on OS has not been conclusively established in clinical trials; furthermore, CAB is associated with considerable side effects, including liver damage, hot flushes and breast pain[4,5]

ADT = androgen deprivation therapy; CAB = complete androgen blockade; HRQoL = health-related quality of life; mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration sensitive prostate cancer

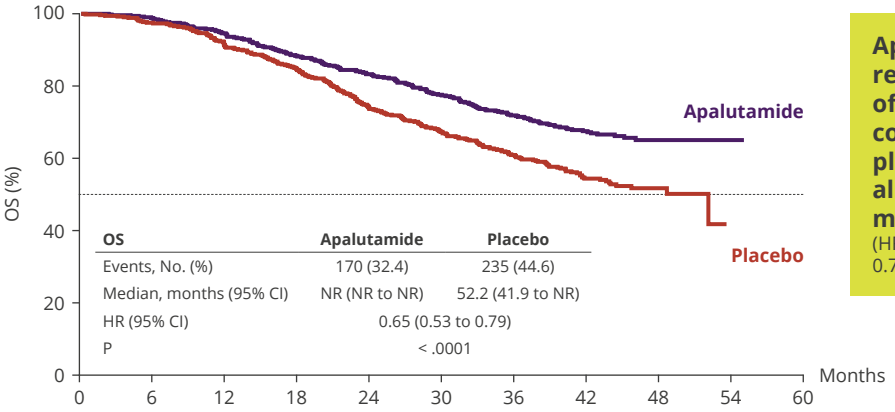
1. Albertsen PC, Aaronson NK, Muller MJ, Keller SD, Ware JE, Jr. Health-related quality of life among patients with metastatic prostate cancer. Urology. 1997;49(2):207-216; discussion 216-207.
2. Burbridge C, Randall JA, Symonds T, et al. Qualitative study to understand the emotional response to a metastatic diagnosis in castration-resistant prostate cancer. Journal of Clinical Oncology. 2018;36(30_suppl):201-201.
3. European Association of Urology. EAU - EANM - ESTRO - ESUR - SIOG Guidelines on Prostate Cancer. 2020.
4. Chen XQ, Huang Y, Li X, et al. Efficacy of maximal androgen blockade versus castration alone in the treatment of advanced prostate cancer: a retrospective clinical experience from a Chinese medical centre. Asian J Androl. 2010;12(5):718-727.
5. Pu YP UH, Ye D, et al. United in Fighting for PrOstate Cancer Registry (UFO). Preliminary results of M1 cases from a large, multi-center, prospective, longitudinal cohort study in Asia. 38th Congress of the Société Internationale d'Urologie (SIU); 2018; Seoul, South Korea.

EFFICACY

Apalutamide + ADT improves overall survival by reducing the risk of death by over a third (35%) compared with ADT alone in all patients with mCSPC

Treatment with apalutamide + ADT allows you to delay disease progression or death by 52% compared with ADT alone in patients with mCSPC, regardless of tumour burden or risk stratification

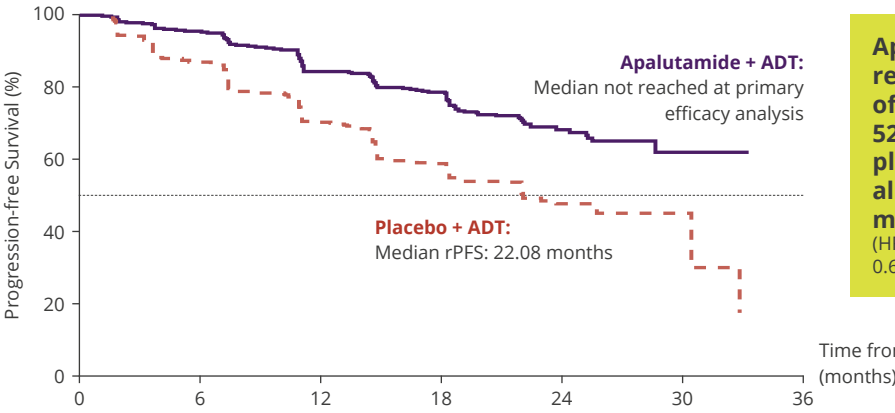
Significant overall survival advantage seen for Apalutamide + ADT compared to ADT alone in final analysis of TITAN trial



OS	Apalutamide	Placebo
Events, No. (%)	170 (32.4)	235 (44.6)
Median, months (95% CI)	NR (NR to NR)	52.2 (41.9 to NR)
HR (95% CI)	0.65 (0.53 to 0.79)	
P	< .0001	

Apalutamide + ADT reduced the risk of death by 35% compared with placebo + ADT in all patients with mCSPC
(HR: 0.65; 95% CI: 0.53, 0.79; nominal p<0.0001)[1]

Radiographic progression-free survival in the TITAN trial



Apalutamide + ADT reduced the risk of progression by 52% compared with placebo + ADT in all patients with mCSPC
(HR: 0.48; 95% CI: 0.39, 0.60; p<0.001)[2]

ADT = androgen deprivation therapy; CAB = complete androgen blockade; CI = confidence interval; HR = hazard ratio; mCSPC = metastatic castration sensitive prostate cancer; OS = overall survival

1. Chi KN, Chowdhury S, Bjartell A, et al. Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study. Journal of Clinical Oncology. 2021:JCO. 20.03488.
2. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. New England Journal of Medicine. 2019;4(381(1)):13-24.

EFFICACY

Early treatment with apalutamide at the mCSPC stage leads to better long-term outcomes than delaying specialised treatment until mCRPC

Apalutamide + ADT rapidly reduces patients' PSA levels and significantly delays PSA progression compared with ADT alone

Apalutamide + ADT significantly delays the development of castration resistance and progression to mCRPC

At the final analyses of the phase III TITAN trial:

PFS2 ▼38%

Results indicate that receiving apalutamide + ADT early in the treatment pathway can **reduce the risk of progression on first subsequent treatment**. (HR: 0.62; 95% CI: 0.51, 0.75; nominal p<0.0001)[1]

PSA progression ▼73%

Apalutamide + ADT **reduced the risk of PSA progression by 73%** compared with placebo + ADT (HR: 0.27; 95% CI: 0.22, 0.33; nominal p<0.0001)[1]

Progression to mCRPC ▼65%

Apalutamide + ADT **reduced the risk of progression to mCRPC by 65%** compared with placebo + ADT(HR: 0.34; 95% CI: 0.29, 0.41; nominal p<0.0001)[2]

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration sensitive prostate cancer; OS = overall survival; PFS2 = disease progression on first subsequent therapy; PSA = prostate-specific antigen

1. Chi KN, Chowdhury S, Bjartell A, et al. Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study. Journal of Clinical Oncology. 2021:JCO. 20.03488.
2. Janssen. Time to metastatic castration-resistance prostate cancer in the TITAN trial (Data on file). 2020.

EFFICACY

Apalutamide is more effective than other available treatments for patients with mCSPC

Overall survival (OS)

Based on the updated Janssen NMA using data-cuts closest to the TITAN final analysis (scenario 2)

Apalutamide + ADT has the **highest probability of providing a greater OS benefit** than CAB, D+ADT, ADT alone, AA+P+ADT and ENZA+ADT in patients with mCSPC[1]

Comparator	Median HR [95%CrI]	P(best)
Apalutamide + ADT	--	**44.83%**
AA+P+ADT	0.992 [0.755; 1.303]	40.12%
D+ADT	0.882 [0.695; 1.119]	2.929%
ENZA+ADT	0.803 [0.502; 1.287]	12.11%
ADT alone	0.651 [0.534; 0,793]	0.000%
NSAA+ADT	0.539 [0.315; 0.917]	0.018%

Apalutamide has a higher probability of being the best treatment for improving OS than enzalutamide

Radiographic progression-free survival (rPFS)

Based on the original Janssen NMA using data-cuts closest to the TITAN IA (scenario 1)

Apalutamide + ADT has the **highest probability of providing a greater rPFS benefit** than D+ADT and ADT alone; comparisons with CAB were not possible for rPFS[1]

Comparator	Median HR [95%CrI]	P(best)
Apalutamide + ADT	--	**98.67%**
D+ADT	0.702 [0.513; 0.960]	1.329%
ADT alone	0.484 [0.391; 0.600]	0.000%

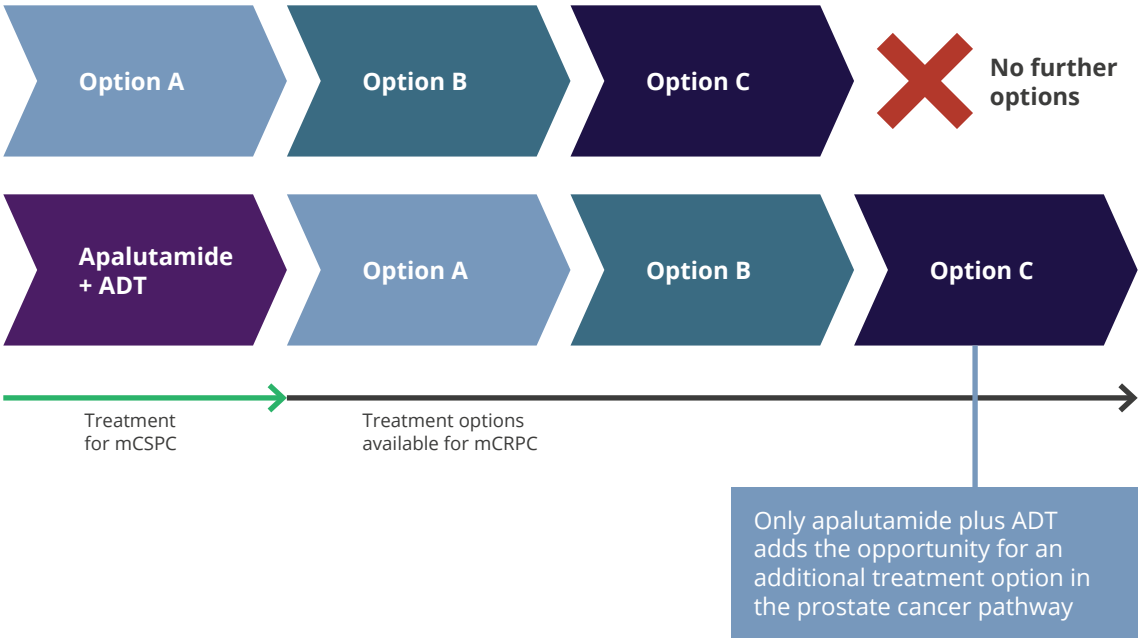
AA = abiraterone acetate; ADT = androgen deprivation therapy; CAB = complete androgen blockade; CI = confidence interval; D = docetaxel; ENZA = enzalutamide; HR = hazard ratio; mCSPC = metastatic castration sensitive prostate cancer; NMA = network meta-analysis; NSAA= Nonsteroidal antiandrogen; OS = overall survival; P = prednisone; rPFS = radiographic progression-free survival

1. Janssen. Network meta-analysis of apalutamide in the treatment of patients with Metastatic Hormone Sensitive Prostate Cancer (mHSPC) - Summary of Results TITAN FA update. (data on file). 2021.

EFFICACY

By prescribing apalutamide in mCSPC, all other treatment options are preserved for the mCRPC disease stage

By **introducing apalutamide** into the prostate cancer treatment pathway early, patients gain an **additional treatment option** to improve their chances of survival **while retaining additional specialised treatment options** for late disease (mCRPC)



In the phase III TITAN trial, treatment with apalutamide + ADT significantly reduced the risk of subsequent systemic therapy for prostate cancer by 61% compared with placebo + ADT in patients with mCSPC (HR: 0.390; 95% CI: 0.302, 0.503; p<0.0001)[1]

mCRPC = metastatic castration-resistant prostate cancer; mCSPC = metastatic castration sensitive prostate cancer

1. Janssen. Time to First Subsequent Systemic Therapy for Prostate Cancer - Stratified Analysis; Intent-to-treat Population (Study 56021927PCR3002). (data on file). 2019.

DOSING

Apalutamide can be used immediately in all mCSPC patients without the need for risk/volume stratification testing or tumour burden assessments

Apalutamide is a convenient once-daily oral treatment with no need for co-administration of corticosteroids, dose adjustments for renal or hepatic impairment, or food restrictions

The phase III TITAN trial demonstrated that treatment with apalutamide + ADT provides a benefit in all men with mCSPC, regardless of risk stratification and tumour burden[1,2]

Treatment with apalutamide is simple for the patient: the oral tablet can be taken at home and only requires once-daily administration[3,4]

Unlike AA+P, apalutamide does not require co-administration of corticosteroids which require monitoring for mineralocorticoid excess, adrenocortical insufficiency and hepatotoxicity, and are associated with additional AEs[3-5]

Treatment with apalutamide is not associated with any food restrictions and can be taken with or without food[3-5]

AA = abiraterone acetate; AE = adverse event; P = prednisone

1. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. New England Journal of Medicine. 2019;4(381(1)):13-24.
2. Janssen. Data on file. Topline results: A phase 3 randomized, placebo-controlled, double-blind study of apalutamide plus androgen deprivation therapy (ADT) versus ADT in subjects with metastatic hormone-sensitive protstate cancer (mHSPC). 15 October 2020.
3. Food and Drug Administration (FDA). ERLEADA (apalutamide) tablets, for oral use. Prescribing Information. November 2020.
4. Janssen. Erleada Summary of Product Characteristics. December 2020.
5. Janssen. Prescribing Information (Zytiga). 2020; http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/ZYTIGA-pi.pdf. Accessed January 2021.

HRQoL

Apalutamide + ADT maintains patients' HRQoL allowing them to continue with their daily activities for longer than with ADT alone

Apalutamide is a convenient once-daily treatment with no need for co-administration of corticosteroids, dose adjustments for renal or hepatic impairment, or food restrictions

Patients' responses to the **'I am able to work'** FACT-G item in the TITAN trial indicated that the addition of apalutamide to ADT did not affect patients' ability to work[2]

In the phase III TITAN trial, treatment with apalutamide + ADT maintained HRQoL in patients with mCSPC at a level similar to that observed in the general population[1]; patients treated with apalutamide + ADT were able to maintain their functional, social and emotional well-being[1]

At the FA of the phase III TITAN trial, apalutamide + ADT reduced the risk of pain progression by 13% (HR: 0.87; 95% CI: 0.70, 1.08; nominal p=0.1966) and reduced the risk of chronic opioid use by 21% compared with placebo + ADT (HR: 0.79; 95% CI: 0.58, 1.09; nominal p=0.1563)[3]

Treatment with apalutamide + ADT reduced the risk of deterioration in patient's ability to care for themselves and in their daily activity and physical ability compared with placebo + ADT (based on risk of ECOG PS deterioration; HR: 0.787; 95% CI: 0.600, 1.033; p=0.0842)[2]

The risk of experiencing a skeletal-related event such as symptomatic pathological fracture, spinal cord compression or bone radiation/surgery was reduced by 14% with apalutamide + ADT compared with placebo + ADT at the FA of the TITAN trial (HR: 0.86; 95% CI: 0.62, 1.19; nominal p=0.3608)[3]

ADT = androgen deprivation therapy; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FA = final analysis; HR = hazard ratio; HRQoL = health-related quality of life; mCSPC = metastatic castration sensitive prostate cancer;

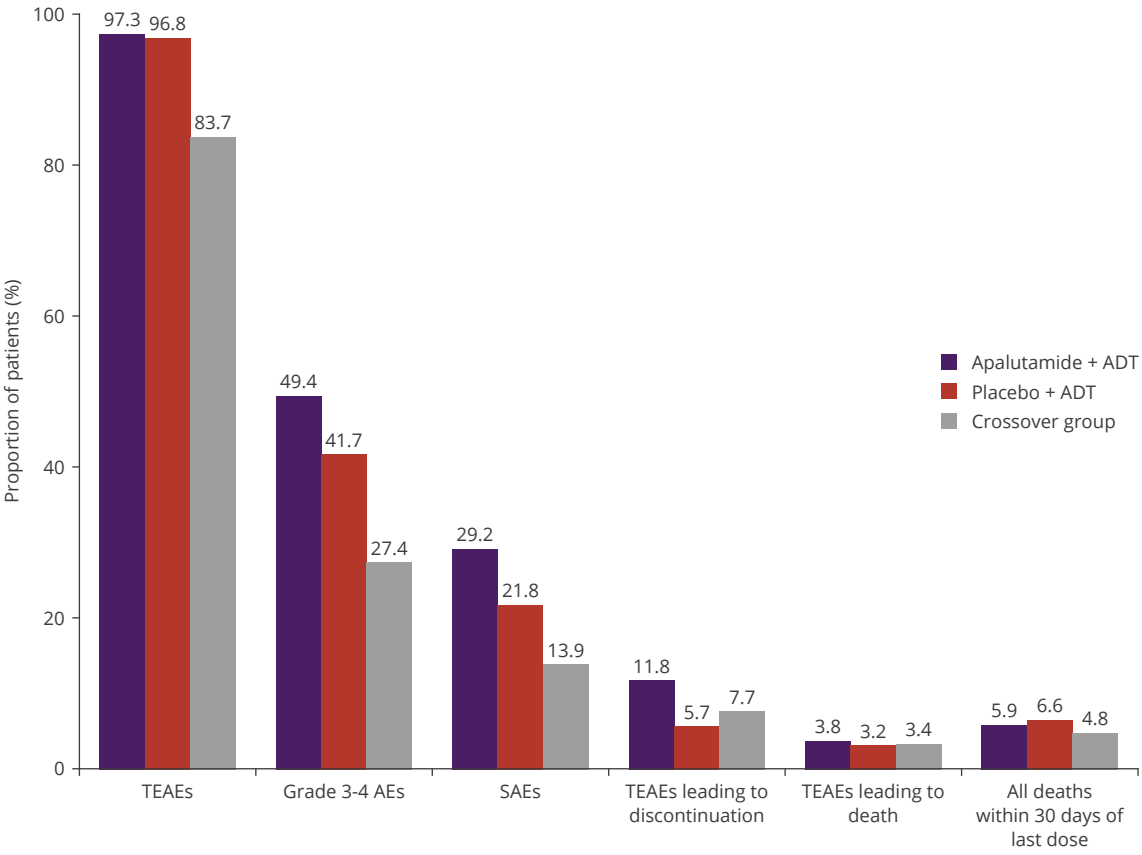
1. Agarwal N, McQuarrie K, Bjartell A, et al. Health-related quality of life after apalutamide treatment in patients with metastatic castration-sensitive prostate cancer (TITAN): a randomised, placebo-controlled, phase 3 study. The Lancet Oncology. 2019;20(11):1518-1530.
2. Janssen. TITAN Interim Clinical Study Report (CSR). 10 April 2019.
3. Janssen. Data on file. Topline results: A phase 3 randomized, placebo-controlled, double-blind study of apalutamide plus androgen deprivation therapy (ADT) versus ADT in subjects with metastatic hormone-sensitive prostate cancer (mHSPC). 15 October 2020.

SAFETY

Apalutamide + ADT has a robust and well-tolerated safety profile with a comparable rate of adverse events and serious adverse events to ADT alone

In the phase III TITAN trial, **similar rates of treatment-related AEs and SAEs were observed with apalutamide + ADT and placebo + ADT** in patients with mCSPC at both the IA and FA, despite a longer median treatment duration on apalutamide than placebo (IA: 20.5 months vs 18.3 months; FA: 39.3 months vs 20.2 months)[1,2]

Safety outcomes in the TITAN trial (final analysis)[2]



The safety/tolerability profile of apalutamide + ADT in patients with mCSPC is consistent with the results of the SPARTAN study in nmCRPC

Note: After the interim analysis, the TITAN trial was unblinded and patients in the placebo + ADT arm were allowed to crossover to the apalutamide + ADT arm; this group is referred to as the crossover group. In total, 208 patients (39.5%) crossed over into the apalutamide + ADT arm.[2]

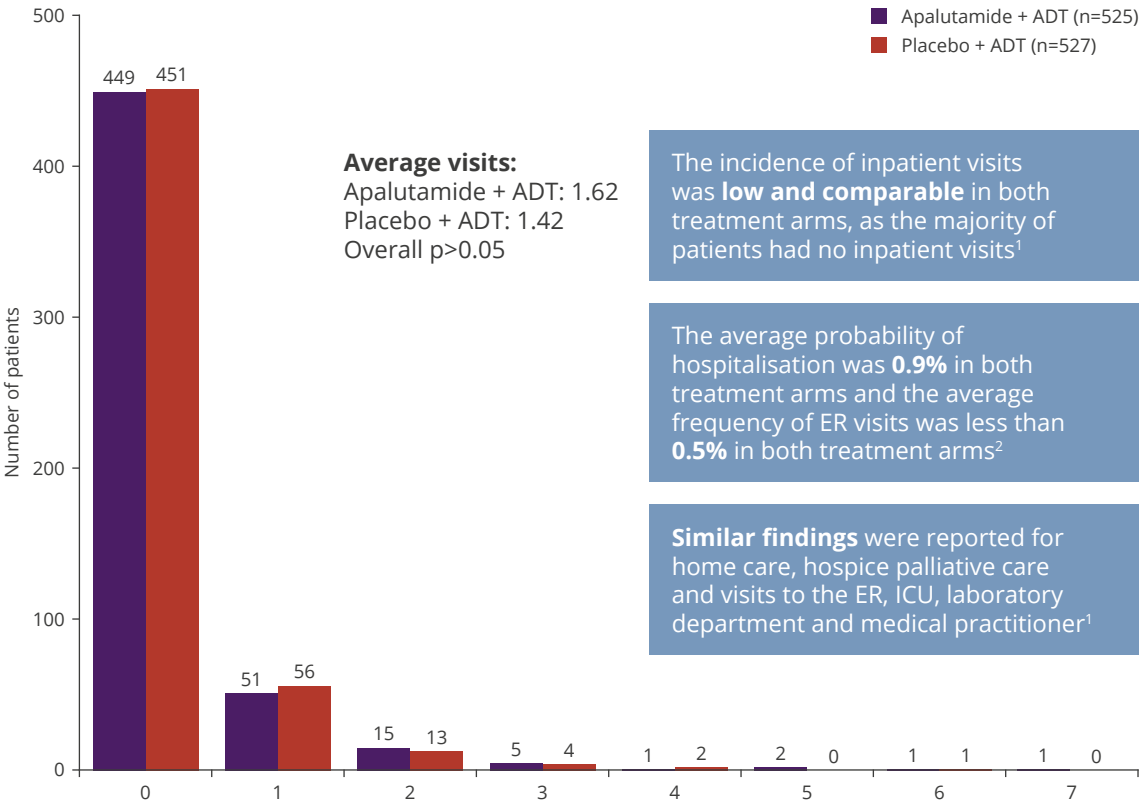
ADT = androgen-deprivation therapy; FA = final analysis; IA = intital analysis; mCSPC = metastatic castration-sensitive prostate cancer; TEAE = treatment-emergent adverse event

1. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. New England Journal of Medicine. 2019;4(381(1)):13-24.
2. Chi KN, Chowdhury S, Bjartell A, et al. Supplementary Materials: Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study. Journal of Clinical Oncology. 2021:JCO. 20.03488.

ECONOMIC VALUE

The addition of apalutamide to ADT does not increase medical resource utilisation, including the frequency of hospitalisations, home care and ER visits

Inpatient visits in each treatment arm of the TITAN trial[1]



Average visits:
Apalutamide + ADT: 1.62
Placebo + ADT: 1.42
Overall p>0.05

The incidence of inpatient visits was **low and comparable** in both treatment arms, as the majority of patients had no inpatient visits[1]

The average probability of hospitalisation was **0.9%** in both treatment arms and the average frequency of ER visits was less than **0.5%** in both treatment arms[2]

Similar findings were reported for home care, hospice palliative care and visits to the ER, ICU, laboratory department and medical practitioner[1]

No significant differences in MRU were found between the apalutamide + ADT and placebo + ADT treatment arms across all resources considered in the analysis[1]

ADT = androgen-deprivation therapy; ER = emergency room; ICU = intensive care unit; MRU = medical resource utilisation

1. Janssen. TITAN IA1 MRU analysis (Data on file). 2019
2. Agarwal N, Graff J, Dearden L, Heeg B, Wigfield P. PCN168 Medical resource utilization (MRU) of apalutamide (apa) plus androgen deprivation therapy (ADT) in non-metastatic castration-resistant prostate cancer (nmCRPC) and metastatic castration-sensitive prostate cancer (mCSPC): results from SPARTAN and TITAN. Value in Health. 2020;23:S52.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