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KEY TAKEAWAYS

With a predicted median OS of 71.5 months, APA can provide up to 32.0 months of additional survival benefit when compared with PBO, supporting early treatment with APA across the broad mHSPC population.

NAVIGATION

KEY TAKEAWAY
CONCLUSIONS
INTRODUCTION
FIGURE 1
Original KM-Plot of TITAN study OS
METHODS
TABLE 1
TITAN Patient Characteristics
RESULTS
TABLE 2
Parametric Predictions APA OS ITT
FIGURE 2
Best fitting Prediction APA OS ITT
TABLE 3
Best fitting OS Predictions TITAN
DISCUSSION
APPENDIX

Presented by Agarwal at ASCO GU; January 25–27, 2024; San Francisco, CA, US

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CONCLUSIONS

- The findings of this study report the first survival extrapolations beyond trial follow-up of a clinical intervention studied in mHSPC which has not reached median OS.
- The predicted OS medians for the overall mHSPC population and for all subpopulations were higher for the APA arm compared with the PBO arm.
- LVD patients treated with APA were predicted to benefit from a median OS of up to 113.1 months translating into an additional 5.5 years of survival.
- Even for patients with the worst prognosis (HVD synchronous), predicted median OS with APA is up to 52.1 months, which corresponds to an additional 1.5 years survival benefit.

NAVIGATION

KEY TAKEAWAY
CONCLUSIONS
INTRODUCTION
FIGURE 1
Original KM-Plot of TITAN study OS
METHODS
TABLE 1
TITAN Patient Characteristics
RESULTS
TABLE 2
Parametric Predictions APA OS ITT
FIGURE 2
Best fitting Prediction APA OS ITT
TABLE 3
Best fitting OS Predictions TITAN
DISCUSSION
APPENDIX

Presented by Agarwal at ASCO GU; January 25–27, 2024; San Francisco, CA, US

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INTRODUCTION

- The treatment landscape for metastatic hormone-sensitive prostate cancer (mHSPC) has been shifting in recent years with the availability of new therapies that are administered in combination with androgen deprivation therapy (ADT).[1]
- Apalutamide plus ADT (APA) demonstrated significantly improved overall survival (OS) compared with placebo plus ADT (PBO) for patients with mHSPC in the TITAN study (hazard ratio, 0.65; 95% confidence interval: 0.53, 0.79; P<.0001).[2]
- At the time of final analysis, the median OS was not reached in the APA arm after a median follow-up of 44.0 months, leaving a relevant evidence gap (Figure 1).[2]

NAVIGATION

KEY TAKEAWAY
CONCLUSIONS
INTRODUCTION
FIGURE 1 Original KM-Plot of TITAN study OS
METHODS
TABLE 1 TITAN Patient Characteristics
RESULTS
TABLE 2 Parametric Predictions APA OS ITT
FIGURE 2 Best fitting Prediction APA OS ITT
TABLE 3 Best fitting OS Predictions TITAN
DISCUSSION
APPENDIX

Presented by Agarwal at ASCO GU; January 25–27, 2024; San Francisco, CA, US

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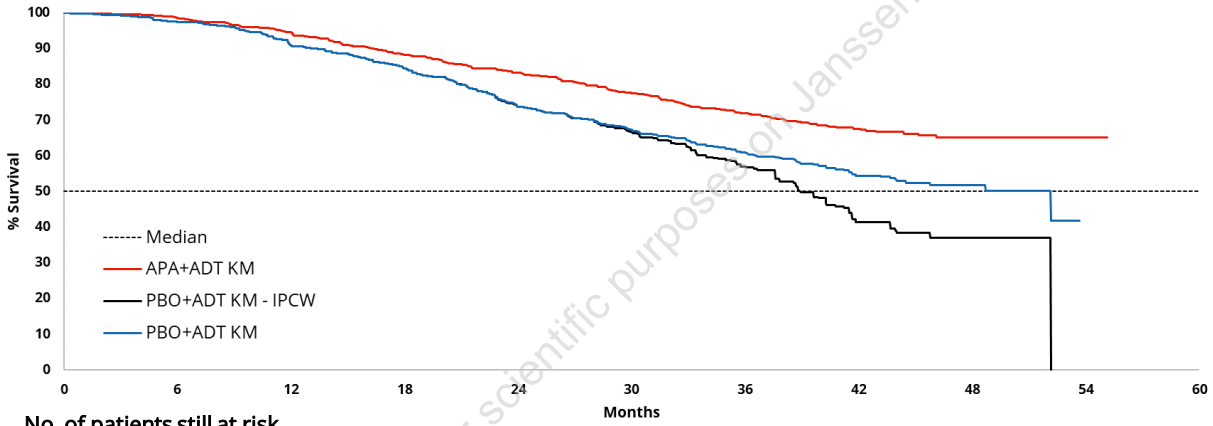
INTRODUCTION

FIGURE 1: Original Kaplan-Meier (KM) plot of OS with and without crossover adjustment from TITAN



No. of patients still at risk

APA - ITT	525	513	489	452	425	394	362	227	52	3
PBO - ITT	527	510	474	436	374	339	301	181	43	0
PBO - IPCW	527	511	475	437	342	210	104	55	18	1

Abbreviations: APA, apalutamide; ADT, androgen deprivation therapy; ITT, intent to treat; IPCW, inverse probability of censoring weighting; KM, Kaplan-Meier; PBO, placebo

Presented by Agarwal at ASCO GU; January 25–27, 2024; San Francisco, CA, US

NAVIGATION

KEY TAKEAWAY
CONCLUSIONS
INTRODUCTION
Figure 1
Original KM-Plot of TITAN study OS
METHODS
TABLE 1
TITAN Patient Characteristics
RESULTS
TABLE 2
Parametric Predictions APA OS ITT
FIGURE 2
Best fitting Prediction APA OS ITT
TABLE 3
Best fitting OS Predictions TITAN
DISCUSSION
APPENDIX

Estimating median overall survival of apalutamide compared with placebo in metastatic hormone-sensitive prostate cancer (mHSPC) populations: statistical extrapolations of the TITAN study

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INTRODUCTION

- Median OS is a relevant and easy-to-understand statistic for patients and healthcare providers to guide treatment decisions. In trials where median OS is not reached, validated survival extrapolation can be applied and median OS can be derived.
- This study aims to estimate the median OS for the APA (n=525) and PBO (n=527) arms beyond the TITAN trial follow-up by fitting validated survival models.
- Given the heterogenous nature of mHSPC in addition to evaluating medians for the overall mHSPC population, several subgroups of clinical interest were also examined: low-volume disease (LVD; better prognosis) and high-volume disease (HVD; worse prognosis), HVD synchronous (M1 at diagnosis), and HVD metachronous (M0 at diagnosis). Patients with mHSPC with HVD synchronous represent the population with the worst prognosis.

NAVIGATION

KEY TAKEAWAY
CONCLUSIONS
INTRODUCTION
FIGURE 1
Original KM-Plot of TITAN study OS
METHODS
TABLE 1
TITAN Patient Characteristics
RESULTS
TABLE 2
Parametric Predictions APA OS ITT
FIGURE 2
Best fitting Prediction APA OS ITT
TABLE 3
Best fitting OS Predictions TITAN
DISCUSSION
APPENDIX

Presented by Agarwal at ASCO GU; January 25–27, 2024; San Francisco, CA, US

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METHODS

- Upon final analysis of the primary endpoint (radiographic progression-free survival), treatment was unblinded and patients were allowed to cross over from the PBO arm and receive APA (39%; 208/527). Crossover adjustments such as inverse probability of censoring weighting (IPCW) were therefore required and applied to the PBO arm.

- OS was obtained for the ITT population treated with APA or PBO, with or without crossover adjustment using IPCW, as well as for the LVD, HVD, HVD synchronous, and HVD metachronous subgroups.2,4,5

NAVIGATION

KEY TAKEAWAY
CONCLUSIONS
INTRODUCTION
FIGURE 1
Original KM-Plot of TITAN study OS
METHODS
TABLE 1
TITAN Patient Characteristics
RESULTS
TABLE 2
Parametric Predictions APA OS ITT
FIGURE 2
Best fitting Prediction APA OS ITT
TABLE 3
Best fitting OS Predictions TITAN
DISCUSSION
APPENDIX

Presented by Agarwal at ASCO GU; January 25–27, 2024; San Francisco, CA, US

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METHODS

TABLE 1: Patient characteristics in the TITAN study [3]

- Standard parametric models (Weibull, exponential, log-normal, log-logistic, generalized gamma, and Gompertz) were fit to the patient-level data as outlined in National Institute for Health and Care Excellence Technical Support Document 14.[6] Tests for proportional hazards were conducted, and models were individually fitted to each treatment arm and subpopulation.
- Model fits were analyzed based on statistical fits (with Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC] rankings), visual fits, and clinical plausibility.[6]
- Survival models were limited based on a weighted average of the general population mortality rates recorded in the top 5 countries in which patients were recruited (i.e., Russian Federation [n=131; 12.5%], Ukraine [n=102; 9.7%], China [n=94; 8.9%], Brazil [n=92; 8.7%], United States [n=92; 8.7%]) to avoid clinically implausible extrapolations.
- Incremental survival was derived between the predicted APA arm and predicted PBO arm with IPCW crossover adjustment to ensure consistency in terms of the methodological approach used.

	APA + ADT	PBO + ADT
N	525	527
Age, years		
Median (range)	69.0 (45–94)	68.0 (43–90)
Metastatic stage at initial diagnosis, n (%)		
M0	85 (16.2)	59 (11.2)
M1	411 (78.3)	441 (83.7)
Mx	29 (5.5)	27 (5.1)
ECOG PS score, n (%)		
0	328 (62.5)	348 (66.0)
1	197 (37.5)	178 (33.8)
2	0	1 (0.2)
Gleason score at initial diagnosis, n (%)		
<7	41 (7.8)	39 (7.4)
7	133 (25.3)	130 (24.7)
>7	351 (66.9)	358 (67.9)
Disease volume, n (%)		
Low	200 (38.1)	192 (36.4)
High	325 (61.9)	335 (63.6)

Abbreviations: APA, apalutamide plus androgen deprivation therapy; ECOG, Eastern Cooperative Oncology Group; PBO, placebo plus androgen deprivation therapy; PS, performance status

NAVIGATION

KEY TAKEAWAY
CONCLUSIONS
INTRODUCTION
FIGURE 1 Original KM-Plot of TITAN study OS
METHODS
TABLE 1: TITAN Patient Characteristics
RESULTS
TABLE 2 Parametric Predictions APA OS ITT
FIGURE 2 Best fitting Prediction APA OS ITT
TABLE 3 Best fitting OS Predictions TITAN
DISCUSSION
APPENDIX

Presented by Agarwal at ASCO GU; January 25–27, 2024; San Francisco, CA, US

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RESULTS

- For the analyses conducted in the ITT population, the log-normal distribution had the best statistical (i.e., table 2; lowest AIC 1,917; BIC 1,926) and visual fit to the trial data for APA.
- The extrapolated median OS predicted by the remaining parametric models for APA ranged from 62.4 months using a Gompertz distribution, to 78.1 months using an exponential model.

TABLE 2: Predicted median OS from parametric extrapolations in months – APA; ITT

Parametric distribution	Median OS	AIC	BIC
Weibull	63.5	1,927	1,936
Exponential	78.1	1,948	1,953
Log-normal	71.5	1,917	1,926
Log-logistic	66.8	1,923	1,931
Gompertz	62.4	1,940	1,949
Generalized gamma	74.7	1,919	1,932

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival

Presented by Agarwal at ASCO GU; January 25–27, 2024; San Francisco, CA, US

NAVIGATION

KEY TAKEAWAY
CONCLUSIONS
INTRODUCTION
FIGURE 1
Original KM-Plot of TITAN study OS
METHODS
TABLE 1
TITAN Patient Characteristics
RESULTS
TABLE 2
Parametric Predictions APA OS ITT
FIGURE 2
Best fitting Prediction APA OS ITT
TABLE 3
Best fitting OS Predictions TITAN
DISCUSSION
APPENDIX

Estimating median overall survival of apalutamide compared with placebo in metastatic hormone-sensitive prostate cancer (mHSPC) populations: statistical extrapolations of the TITAN study

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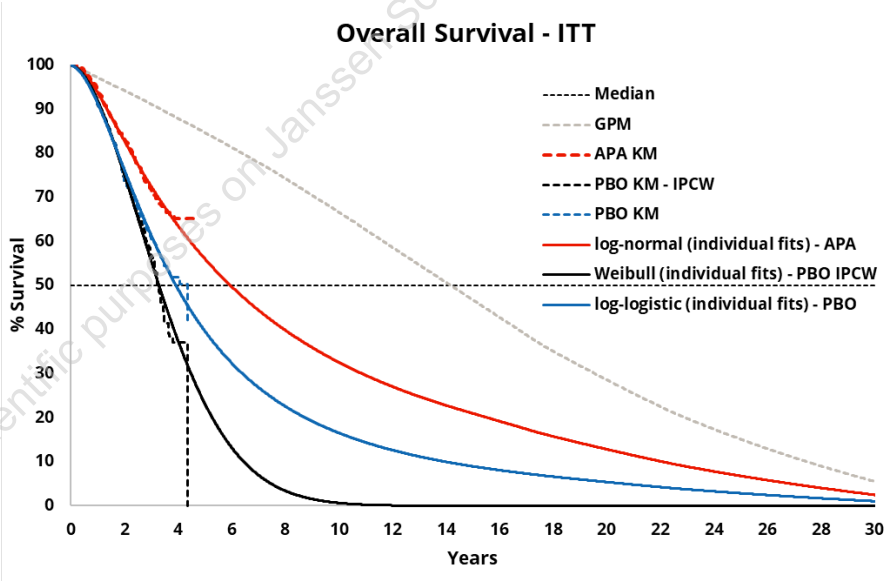
RESULTS

- Based on the parametric extrapolations, median OS was predicted to be 71.5 months for the APA arm in the ITT population (see Table 3 and Figure 2) representing a 32-month increase in OS when compared to predicted PBO
- The predicted median OS for APA in the LVD subgroup was 113.1 months compared with 47.3 months predicted OS in the PBO arm representing a 65.8-month difference in median OS between arms.
- For APA in HVD subgroups (synchronous and metachronous) there is a consistent predicted median OS of 52 months.

FIGURE 2: KM-plot best statistically fitting extrapolations of OS - ITT



Abbreviations: APA, apalutamide; GPM, general population mortality; ITT, intent to treat; IPCW, inverse probability of censoring weighting; KM, Kaplan-Meier; OS, overall survival; PBO, placebo

NAVIGATION

KEY TAKEAWAY
CONCLUSIONS
INTRODUCTION
FIGURE 1 Original KM-Plot of TITAN study OS
METHODS
TABLE 1 TITAN Patient Characteristics
RESULTS
TABLE 2 Parametric Predictions APA OS ITT
FIGURE 2 Best fitting Predictions APA OS ITT
TABLE 3 Best fitting OS Predictions TITAN
DISCUSSION
APPENDIX

Presented by Agarwal at ASCO GU; January 25–27, 2024; San Francisco, CA, US

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RESULTS

TABLE 3: Actual and best fit median OS extrapolations in TITAN

Population	Median OS (months)					
	Actual			Predicted (best fit)		
	APA + ADT	PBO + ADT		APA + ADT	PBO + ADT	
		Unadjusted	IPCW		Unadjusted	IPCW
ITT	NE	52.2	38.8	71.5[c]	47.1[d]	39.5[a]
LVD	NE	NE	45.8	113.1[d]	63.0[a]	47.3[e]
HVD	NE	38.7	35.3	51.9[c]	38.3[c]	33.8[a]
HVD synchronous	NE	36.7	34	52.1[c]	37.7[c]	33.4[a]
HVD metachronous	NE	39.6	38.6	52.0[d]	39.1[c]	33.2[d]

Best-fit parametric distribution: a - Weibull; b - exponential; c - log-normal; d - log-logistic; e - Gompertz
Abbreviations: ADT, androgen deprivation therapy; APA, apalutamide plus androgen deprivation therapy; HVD, high-volume disease; IPCW, inverse probability of censoring weighting; ITT, intent to treat; LVD, low-volume disease; NE, not estimable; PBO, placebo plus androgen deprivation therapy
*Difference based on predicted unadjusted median OS PBO estimate.

NAVIGATION

KEY TAKEAWAY
CONCLUSIONS
INTRODUCTION
FIGURE 1 Original KM-Plot of TITAN study OS
METHODS
TABLE 1 TITAN Patient Characteristics
RESULTS
TABLE 2 Parametric Predictions APA OS ITT
FIGURE 2 Best fitting Prediction APA OS ITT
TABLE 3 Best fitting OS Predictions TITAN
DISCUSSION
APPENDIX

Presented by Agarwal at ASCO GU; January 25–27, 2024; San Francisco, CA, US

Estimating median overall survival of apalutamide compared with placebo in metastatic hormone-sensitive prostate cancer (mHSPC) populations: statistical extrapolations of the TITAN study

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DISCUSSION

- While results of this extrapolation study should not be equated to those of a clinical trial, its external validity is underlined when comparing the resulting PBO extrapolations i.e., ITT IPCW 39.5 months with the actual ITT crossover adjusted 38.8 months in TITAN.[2]
- This analysis highlights the benefit of APA translating into 32 months (>2.5 years) longer survival across the broad mHSPC population. This benefit is seen in LVD patients (additional 65.8 months or 5.5 years), as well as HVD synchronous patients (additional 18.7 months or >1.5 years) who typically experience the worst prognosis amongst the mHSPC population.

Presented by Agarwal at ASCO GU; January 25–27, 2024; San Francisco, CA, US

NAVIGATION

KEY TAKEAWAY
CONCLUSIONS
INTRODUCTION
FIGURE 1
Original KM-Plot of TITAN study OS
METHODS
TABLE 1
TITAN Patient Characteristics
RESULTS
TABLE 2
Parametric Predictions APA OS ITT
FIGURE 2
Best fitting Prediction APA OS ITT
TABLE 3
Best fitting OS Predictions TITAN
DISCUSSION
APPENDIX

Estimating median overall survival of apalutamide compared with placebo in metastatic hormone-sensitive prostate cancer (mHSPC) populations: statistical extrapolations of the TITAN study

Neeraj Agarwal,[1] Anders Bjartell,[2] Álvaro Juárez,[3] Ronja Kerßenboom[4] (rkerenbo@its.jnj.com), Nolen Perualila,[5] Peter Wigfield,[6] Kim N. Chi[7]

APPENDIX

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DISCLOSURES:

The authors report relationships/financial interest in/relative to as follows: NA: Bayer, Bristol-Myers Squibb, Takeda, Pfizer, Exelixis, Amgen, AstraZeneca, Calithera Biosciences, Celldex, Eisai, Genentech, Immunomedics, Janssen, Merck, Lilly, Nektar, ORIC Pharmaceuticals, crispr therapeutics, Arvinas, Gilead Sciences; AB: Accord, Astellas, Bayer, Glactone Pharma, AstraZeneca, Incyte, Ipsen, Janssen, Merck, Novartis, SAMNordic, Ferring, LIDDS Pharma, WntResearch; AJ: Astellas, Bayer, Janssen; KNC: ESSA, ASTELLAS PHARMA, Janssen, Sanofi, Amgen, Bayer, AstraZeneca, Roche, POINT Biopharma, Daiichi Sankyo, Merck, Constellation Pharmaceuticals, Novartis, Bristol-Myers Squibb; NP and RK are employees of Janssen Research & Development and may hold stock in Johnson & Johnson

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Presented by Agarwal at ASCO GU; January 25–27, 2024; San Francisco, CA, US

NAVIGATION