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Apalutamide (prostate cancer) –

Addendum to Commission A19-09[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ADT	androgen deprivation therapy
AEs	adverse events
CTCAE	Common Terminology Criteria for Adverse Events
EQ-5D	European Quality of Life-5 Dimensions
FACT-P	Functional Assessment of Cancer Therapy – Prostate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
nmCRPC	non-metastatic castration-resistant prostate cancer
PT	preferred term
SAEs	serious adverse events
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
OC	System Organ Class
VAS	visual analogue scale

1 Background

On 12 June 2019, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-09 (Apalutamide – Benefit assessment according to §35a Social Code Book V) [1].

In its written comments from 23 May 2019 [2], the pharmaceutical company (hereinafter referred to as "the company") submitted further analyses on the SPARTAN study, which went beyond the information provided in the dossier [3,4].

The G-BA's commission comprised the following aspects:

- Assessment of the data of the subsequently submitted data cut-off of 1 February 2019[2]. On 4 July 2019, the G-BA specified the commission stating that the data of the subsequently submitted data cut-off were only to be assessed when the validity of this data cut-off was confirmed.
- Assessment of subsequently submitted event time analyses on serious adverse events (SAEs) including the fatal SAEs on the primary data cut-off of 19 May 2017.
- Presentation of the responder analyses of the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D) (EQ-5D VAS) on the primary data cut-off of 19 May 2017 and on the subsequently submitted data cut-off of 1 February 2019.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

[2] The text of the G-BA's commission refers to the data cut-off of 3 April 2019. This date specified by the company is presumably the date of the database closure (for reasons, see Section 2.1).

2 Assessment

2.1 Data of the subsequently submitted data cut-off of 1 February 2019

Data cut-off not usable

With its written comments, the company subsequently submitted data on a further data cut-off of the SPARTAN study. This data cut-off is not usable for the benefit assessment. This is justified below:

The data cut-off had not been planned a priori and it cannot be assumed that it was conducted without knowledge of the results. In its written comments [2], the company stated that the subsequently submitted data cut-off had been conducted on 3 April 2019 and included data up to and including the clinical data cut-off of 1 February 2019. According to the company, the data cut-off had been conducted after formal adjustment of the study protocol (3 March 2019) and the statistical analysis plan (SAP) (4 March 2019) [2]. The time point at which the data cut-off was actually conducted is unclear, because the company did not use the terms "data cut-off" and "clinical cut-off" synonymously. However, as the company, in its comments, indicated "19 May 2017" as clinical cut-off also for the first data cut-off, and moreover designated the date "3 April 2019" as database lock (corresponds to the database closure) in the oral hearing [5], it must be assumed that the date of the subsequently submitted data cut-off is 1 February 2019, while 3 April 2019 is the date of the database closure. Therefore, the data cut-off subsequently submitted by the company is consistently referred to as data cut-off of 1 February 2019 in the present addendum.

According to the adjusted study protocol and the statistical analysis plan, the new second data cut-off was to take place as soon as 65% of the number of events planned for the final analysis of "overall survival" had been achieved. The rationale for this criterion, on which the date of the second data cut-off (1 February 2019) is based, can neither be learned from the company's comment nor from the oral hearing. Moreover, the study protocol and the statistical analysis plan were only adjusted after this date.

Following the first data cut-off of 19 May 2017, the SPARTAN study was unblinded on 22 July 2017. Thereafter, patients who were still being treated in the placebo arm could switch to treatment with apalutamide. According to the company, the remaining 76 (19%) patients made this treatment switch. According to the study documents, 119 patients were still being treated in the placebo arm at the time point of the first data cut-off (19 May 2017). 43 further patients result from the difference between these figures. There is no information available on these patients, e.g. whether they discontinued treatment between 19 May 2017 and 22 July 2017.

In summary, the subsequently submitted data cut-off of 1 February 2019 is considered to be unusable for the benefit assessment for the reasons described above. However, the results of this data cut-off are hereinafter presented and described as supplementary information; the corresponding Kaplan-Meier curves are presented as supplementary information in Appendix A.

Further biasing aspects

Irrespective of the usability of the subsequently submitted data cut-off, there were further potentially biasing aspects for the results of isolated outcomes besides the factors described in the benefit assessment. For instance, the switch of 19% of the patients in the placebo arm to treatment with apalutamide after unblinding of the study might have an impact on the results (ITT analysis) of the outcomes "overall survival" and "symptomatic progression". Moreover, after the study had been unblinded, disease progression including the symptoms was no longer recorded systematically, but based on the physician's decision. As explained hereinafter, there were no further biasing aspects for outcomes that had no longer been recorded in the placebo arm after the treatment switch (health status, health-related quality of life, AEs).

No additional relevant information for the outcomes "AEs", "health status" and "health-related quality of life"

For the outcomes of the category "side effects", the chosen time point of a data cut-off conducted after unblinding had no relevant influence on the results, because no patient of the placebo arm was under observation upon or shortly after unblinding. Comparison via the hazard ratio only refers to the period in which both arms still included patients at risk. The results on later data cut-offs can thus not differ considerably from those on the first data cut-off. This can also be recognized from the specific results. For the outcome "general disorders and administration site conditions" (severe AEs with Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) alone, there is a qualitative change regarding the statistical significance; the result is no longer statistically significant.

Follow-up periods of up to 12 months were possible after treatment discontinuation for the outcomes "health status (EQ-5D VAS)" and "health-related quality of life (Functional Assessment of Cancer Therapy – Prostate [FACT-P])", but the response showed that only few recordings had been added in the further course of the study, i.e. in the approx. 21 months since the first data cut-off. Here as well, the time point of the data cut-off was thus not assumed to have any relevant influence on the respective results. Here as well, there is only little difference between these results and the results of the first data cut-off.

Results

Table 1 shows the data on the course of the study, Table 2 and Table 3 summarize the results on the comparison of apalutamide + androgen deprivation therapy (ADT) with placebo + ADT in patients with non-metastatic castration-resistant prostate cancer (nmCRPC) who have a high risk of developing metastases. Subgroup analyses on the outcome "overall survival" are presented in Table 4. Kaplan-Meier curves on the presented event time analyses can be found in Appendix A.

Table 1: Information on the course of the study – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT

Study **Duration of the study phase** **Outcome category**	**Apalutamide + ADT**	**Placebo + ADT**	**Apalutamide + ADT**	**Placebo + ADT**
	Data cut-off: 19 May 2017		Data cut-off: 1 February 2019	
SPARTAN	N = 806	N = 401	N = 806	N = 401
Treatment duration [months]				
Median [min; max]	16.92 [0.1; 42.0]	11.17 [0.1; 37.1]	31.4 [ND]	11.5 [ND]
Mean (SD)	17.34 (9.5)	12.4 (8.0)	ND	ND
Observation period [months]				
Overall survival[a]	ND	ND	ND	ND
Morbidity	ND	ND	ND	ND
health-related quality of life	ND	ND	ND	ND
Side effects	ND	ND	ND	ND

a: For patients in both treatment arms, the median observation period at the first data cut-off of 19 May 2017 was 20.3 months and at the second data cut-off of 1 February 2019 it was about 41 months. There was no information for the individual study arms.

ADT: androgen deprivation therapy; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Table 2: Results (mortality, morbidity, health-related quality of life and side effects, time to event) – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (data cut-off: 1 February 2019)

Study **Outcome category** **Outcome**	**Apalutamide + ADT**		**Placebo + ADT**		**Apalutamide + ADT vs. placebo + ADT**
	N	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
SPARTAN					
Mortality					
Overall survival	806	NA 178 (22.1)	401	NA 107 (26.7)	0.75 [0.59; 0.96]; 0.020
Morbidity					
Symptomatic progression	806	NA [56.28; NC] 129 (16.0)	401	NA 93 (23.2)	0.56 [0.43; 0.73]; < 0.001
Skeletal-related events (pathological fractures, compression of the spinal cord or requirement of a surgical intervention or radiotherapy of the bone)	806	NA 44 (5.5)	401	NA 31 (7.7)	0.60 [0.38; 0.96]; 0.032
Pain progression or deterioration of disease-related symptoms requiring the initiation of a new systemic anticancer therapy	806	NA 64 (7.9)	401	NA 46 (11.5)	0.60 [0.41; 0.88]; 0.008
Clinically significant symptoms due to locoregional tumour progression requiring surgical intervention or radiotherapy	806	NA 39 (4.8)	401	NA 30 (7.5)	0.54 [0.33; 0.87]; 0.012

(continued)

Table 2: Results (mortality, morbidity, health-related quality of life and side effects, time to event) – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (data cut-off: 1 February 2019) (continued)

Study Outcome category Outcome	Apalutamide + ADT N	Apalutamide + ADT Median time to event in months [95% CI] Patients with event n (%)	Placebo + ADT N	Placebo + ADT Median time to event in months [95% CI] Patients with event n (%)	Apalutamide + ADT vs. placebo + ADT HR [95% CI]; p-value[a]
SPARTAN					
Health-related quality of life					
FACT-P					
Total score, deterioration[b] by ≥ 10 points	806	6.60 [5.55; 8.28] 537 (66.6)	401	8.38 [6.47; 12.95] 230 (57.4)	1.04 [0.89; 1.22]; 0.623
Prostate cancer-specific subscale (PCS), deterioration[b] by ≥ 3 points	806	3.84 [3.71; 4.70] 611 (75.8)	401	3.78 [2.86; 4.80] 272 (67.8)	0.97 [0.84; 1.13]
Physical well-being (PWB), deterioration[b] by ≥ 3 points	806	6.57 [5.55; 8.38] 520 (64.5)	401	7.43 [5.59; 11.11] 234 (58.4)	0.97 [0.83; 1.14]
Social/familiar well-being (SWB), deterioration[b] by ≥ 3 points	806	7.49 [5.62; 11.11] 465 (57.7)	401	4.90 [3.84; 8.38] 223 (55.6)	0.87 [0.73; 1.02]
Emotional well-being (EWB), deterioration[b] by ≥ 3 points	806	14.69 [11.07; 18.63] 448 (55.6)	401	14.82 [10.61; 32.99] 181 (45.1)	1.06 [0.89; 1.27]
Functional well-being (FWB), deterioration[b] by ≥ 3 points	806	4.63 [3.78; 5.59] 548 (68.0)	401	6.51 [4.70; 9.27] 229 (57.1)	1.15 [0.98; 1.35]
Side effects					
AEs (supplementary information)	803	0.56 [0.46; 0.72] 781 (97.3)	398	0.76 [0.53; 0.92] 373 (93.7)	–
SAEs	803	36, 83 [31.34; 42.45] 276 (34.4)	398	35.25 [28.19; NC] 100 (25.1)	0.84 [0.67; 1.07]; 0.157
Severe AEs (CTCAE grade ≥ 3)	803	21.85 [18.46; 25.92] 431 (53.7)	398	24.15 [18.43; 29.47] 146 (36.7)	1.11 [0.91; 1.34]; 0.306
Discontinuation due to AEs	803	NA 109 (13.6)	398	NA 29 (7.3)	1.40 [0.92; 2.13]; 0.113

(continued)

Table 2: Results (mortality, morbidity, health-related quality of life and side effects, time to event) – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (data cut-off: 1 February 2019) (continued)

Study **Outcome category** **Outcome**	**Apalutamide + ADT**		**Placebo + ADT**		**Apalutamide + ADT vs. placebo + ADT**
	L	**Median time to event in months [95% CI]** **Patients with event n (%)**	**L**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
SPARTAN					
Specific AEs					
Arthralgia (PT, AEs)	803	NA 152 (18.9)	398	NA 33 (8.3)	1.74 [1.19; 2.54]; 0.005
Skin and subcutaneous tissue disorders (SOC, severe AEs CTCAE grade ≥ 3)	803	NA 52 (6.5)	398	NA 1 (0.3)	23.81 [3.29; 172.30]; 0.002
Nervous system disorders (SOC, AEs)	803	38.87 [31.97; NC] 319 (39.7)	398	NA 93 (23.4)	1.54 [1.22; 1.94]; < 0.001
Renal and urinary disorders (SOC, severe AEs CTCAE grade ≥ 3)	803	NA 60 (7.5)	398	NA [35.48; NC] 46 (11.6)	0.38 [0.25; 0.57]; < 0.001
Hypothyroidism (PT, AEs)	803	NA 58 (7.2)	398	NA 5 (1.3)	4.42 [1.77; 11.07]; 0.002
Injury, poisoning and procedural complications (SOC, SAEs)	803	59.63 [NC; NC] 56 (7.0)	398	NA 6 (1.5)	2.78 [1.19; 6.54]; 0.019

a: HR, CI and p-value: Cox proportional hazards model; stratified by PSADT (≤ 6 months vs. > 6 months), use of bone-preserving substances (yes vs. no), presence of locoregional disease (N0 vs. N1).
b: Deterioration means decrease in score by the respective MID.

ADT: androgen deprivation therapy; AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; FACT-P: Functional Assessment of Cancer Therapy – Prostate; HR: hazard ratio; MID: minimally important difference; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PSADT: prostate specific antigen doubling time; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 3: Results (morbidity, continuous) – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (data cut-off: 19 May 2017 and 1 February 2019)

Study Outcome category	Apalutamide + ADT			Placebo + ADT			Apalutamide + ADT vs. placebo + ADT
Outcome Data cut-off	N[a]	Values at start of study mean (SD)	Change[b] mean (SE)[c]	N[a]	Values at start of study mean (SD)	Change[b] mean (SE)[c]	MD [95% CI][c]; p-value
SPARTAN							
Morbidity							
Health status (EQ-5D VAS[d])							
Data cut-off: 19 May 2017	782	76.28 (17.25)	0.04 (0.41)	386	76.91 (16.88)	-0.18 (0.59)	0.22 [−1.18; 1.62]; 0.757
Data cut-off: 1 February 2019	782	76.28 (17.25)	−0.08 (0.41)	386	76.91 (16.88)	-0.35 (0.59)	0.27 [−1.15; 1.69]; 0.709

a: Number of patients considered in the analysis for the calculation of the effect estimation.
b: The documents supplied by the company provide no information on whether the analysis was conducted for a time point or for a period.
c: Mean and SE as well as MD and p-value (group comparison): MMRM.
d: Higher values indicate better health status; a positive group difference corresponds to an advantage of apalutamide.

ADT: androgen deprivation therapy; CI: confidence interval; EQ-5D European Quality of Life5 Dimensions; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; VAS: visual analogue scale; vs.: versus

Table 4: Subgroups (mortality, time to event) – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (data cut-off: 1 February 2019)

Study Outcome Characteristic Subgroup	Apalutamide + ADT N	Apalutamide + ADT Median time to event in months [95% CI] Patients with event n (%)	Placebo + ADT N	Placebo + ADT Median time to event in months [95% CI] Patients with event n (%)	Apalutamide + ADT vs. placebo + ADT HR [95% CI][a]	Apalutamide + ADT vs. placebo + ADT p-value[a]
SPARTAN						
Overall survival						
Age						
< 65	106	NA 12 (11.3)	43	NA [38.64; NC] 11 (25.6)	0.32 [0.14; 0.77]	0.010
65 to < 75	307	NA [55.79; NC] 67 (21.8)	169	NA 33 (19.5)	1.05 [0.69; 1.60]	0.806
≥ 75	393	NA [52.80; NC] 99 (25.2)	189	49.94 [46.29; NC] 63 (33.3)	0.71 [0.52; 0.97]	0.034
Total					Interaction:	0.045[b]

a: HR, CI and p-value: Cox proportional hazards model; stratified by PSADT (≤ 6 months vs. > 6 months), use of bone-preserving substances (yes vs. no), presence of locoregional disease (N0 vs. N1).
b: Cox proportional hazards model with corresponding interaction term

ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; PSADT: prostate specific antigen doubling time; SAE: serious adverse event; vs.: versus

Positive effects of apalutamide + ADT in comparison with placebo + ADT resulted for the outcomes "overall survival", "symptomatic progression" and "renal and urinary disorders (System Organ Class [SOC], severe AEs with CTCAE grade ≥ 3)". In addition, there was an effect modification by the characteristic "age" for the outcome "overall survival". Accordingly, a significant advantage of apalutamide + ADT was shown for patients aged < 65 years and for patients aged ≥ 75 years. However, no difference between the treatment arms was shown for patients aged between 65 and 75 years; the effect estimation was close to the zero effect. The result of this subgroup analysis is considered not to be meaningfully interpretable, because the result in the mean age stratum differs considerably from those in the older and younger patients.

Negative effects of apalutamide + ADT in comparison with placebo + ADT resulted for "specific AEs", "skin and subcutaneous tissue disorders (SOC, severe AEs with CTCAE grade ≥ 3)", "injury, poisoning and procedural complications (SOC, SAEs)" as well as for the AEs "arthralgia (preferred term [PT])", "nervous system disorders (SOC)" and "hypothyroidism (PT)".

There was no statistically significant difference between the treatment arms for all remaining outcomes.

Summary of the assessment on the data cut-off of 1 February 2019

The results of the subsequently submitted second data cut-off of 1 February 2019 were unsuitable for the benefit assessment. This was due to the unclear rationale for the time point of the data cut-off that had not been scheduled a priori. Irrespective of this, a result that deviates from dossier assessment A19-09 was shown for the outcome "overall survival" alone. Here, the subsequently submitted data cut-off showed a statistically significant advantage of apalutamide + ADT in comparison with placebo + ADT. The overall conclusion on the added benefit of dossier assessment A19-09 [1] has not changed even under consideration of the results of the data cut-off of 1 February 2019. The second data cut-off showed a statistically significant advantage of apalutamide + ADT in comparison with placebo + ADT with the extent "minor" for the outcome "overall survival". However, in the overall consideration, the results led to an indication of considerable added benefit.

2.2 Supplementary analyses at the data cut-off of 19 May 2017

2.2.1 SAEs including fatal events

The company's dossier [3] contained no event time analyses on SAEs comprising both fatal and non-fatal SAEs. The company presented fatal AEs as independent outcome. With the comments, the company presented event time analyses for all SAEs, including fatal events, for the data cut-off of 19 May 2017 [2]. The data are presented in Table 5. Kaplan-Meier curves on this outcome are presented in Appendix A.

Table 5: Subgroups (SAEs, including fatal events) – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (data cut-off: 19 May 2017)

Study Outcome category Outcome	Apalutamide + ADT N	Apalutamide + ADT Median time to event in months [95% CI] Patients with event n (%)	Placebo + ADT N	Placebo + ADT Median time to event in months [95% CI] Patients with event n (%)	Apalutamide + ADT vs. placebo + ADT HR [95% CI]; p-value[a]
SPARTAN					
Side effects					
SAEs	803	NA 204 (25.4)	398	35.25 [25.96; NC] 93 (23.4)	0.80 [0.62; 1.03]; 0.081

a: HR, CI and p-value: Cox proportional hazards model; stratified by PSADT (≤ 6 months vs. > 6 months), use of bone-preserving substances (yes vs. no), presence of locoregional disease (N0 vs. N1).

ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The present analysis of all SAEs (fatal and non-fatal) includes only few additional patients with events in comparison with the analysis of the SAEs without fatal events presented in dossier assessment A19-09 [1]: 5 patients under apalutamide + ADT and 1 patient under placebo + ADT.

At the data cut-off of 19 May 2017, no statistically significant difference between the treatment arms was shown for the outcome “SAEs including fatal events”. This resulted in no hint of greater or lesser harm from apalutamide + ADT in comparison with watchful waiting + ADT.

Regarding the statistically significance, this result does not differ from the result of the outcome “SAEs without fatal events” presented in dossier assessment A19-09 [1].

2.2.2 Presentation of the responder analyses of the EQ-5D VAS

In Module 4 of its dossier [3], the company presented one event time analyses each on the improvement and on the deterioration by ≥ 7 or ≥ 10 points. As already described in dossier assessment A19-09 [1], these responder analyses were unsuitable for the benefit assessment. The analysis of the change since start of the study was thus the analysis relevant for the assessment.

The responder analyses on the EQ-5D VAS on the time to deterioration by 7 or 10 points and the corresponding Kaplan-Meier curves are presented in Appendix C as supplementary information.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure did not change the conclusion on the added benefit of apalutamide from dossier assessment A19-09.

The following Table 6 shows the result of the benefit assessment of apalutamide under consideration of dossier assessment A19-09 [1] and the present addendum.

Table 6: Apalutamide – probability and extent of added benefit

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Adult men with nmCRPC who have a high risk of developing metastases	Watchful waiting while maintaining ongoing conventional ADT[b]	Indication of considerable added benefit
a: Presentation of the ACT specified by the G-BA. b: Surgical castration or medical castration using treatment with GnRH agonists or GnRH antagonists. ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; nmCRPC: non-metastatic castration-resistant prostate cancer		

The G-BA decides on the added benefit.

3 References

The reference list contains citations provided by the company in which bibliographical information may be missing.

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[Demnächst verfügbar unter: https://www.g-ba.de/informationen/nutzenbewertung/437/#beschluesse im Dokument "Zusammenfassende Dokumentation"].

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Appendix A – Kaplan-Meier curves on event time analyses of the data cut-off of 1 February 2019

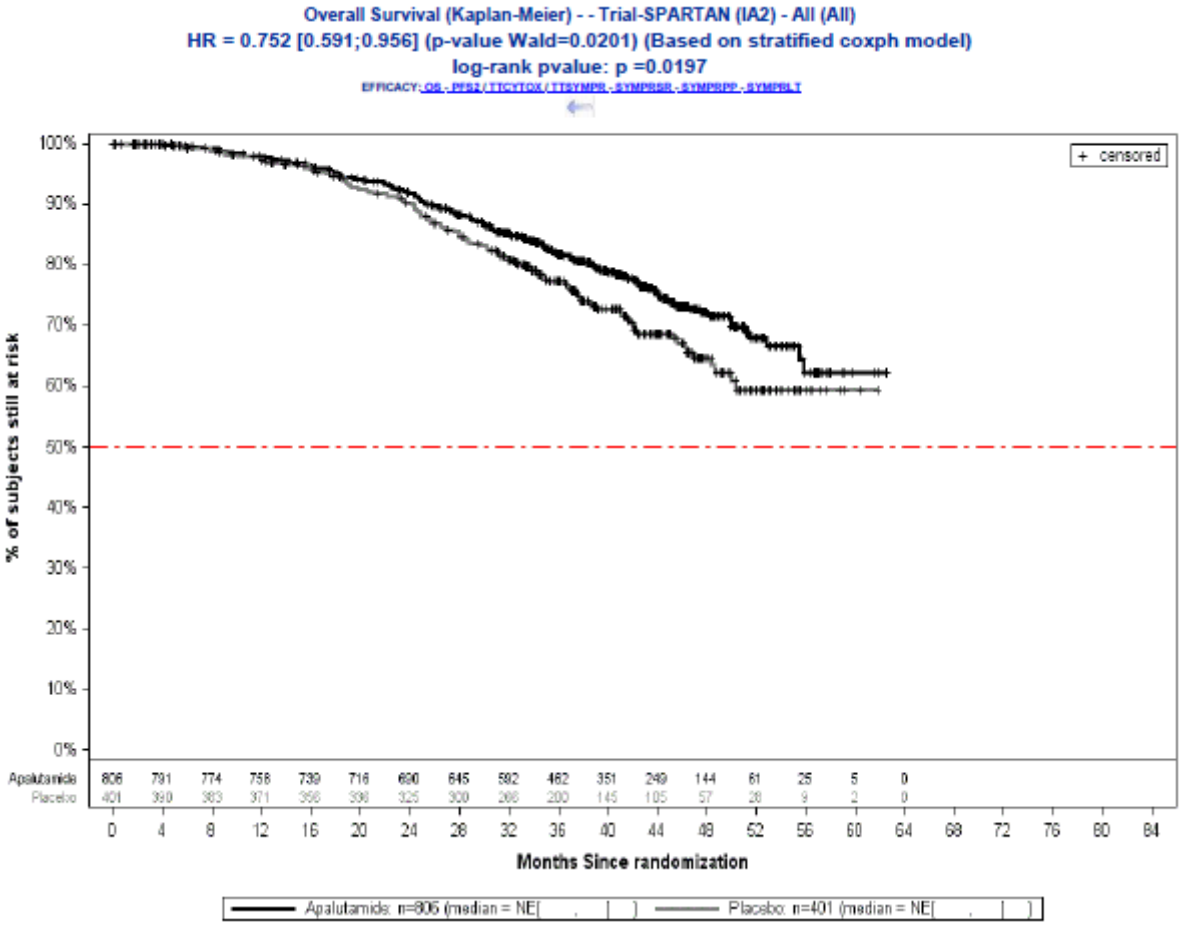

Figure 1: Kaplan-Meier curves for "overall survival" – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (data cut-off: 1 February 2019)

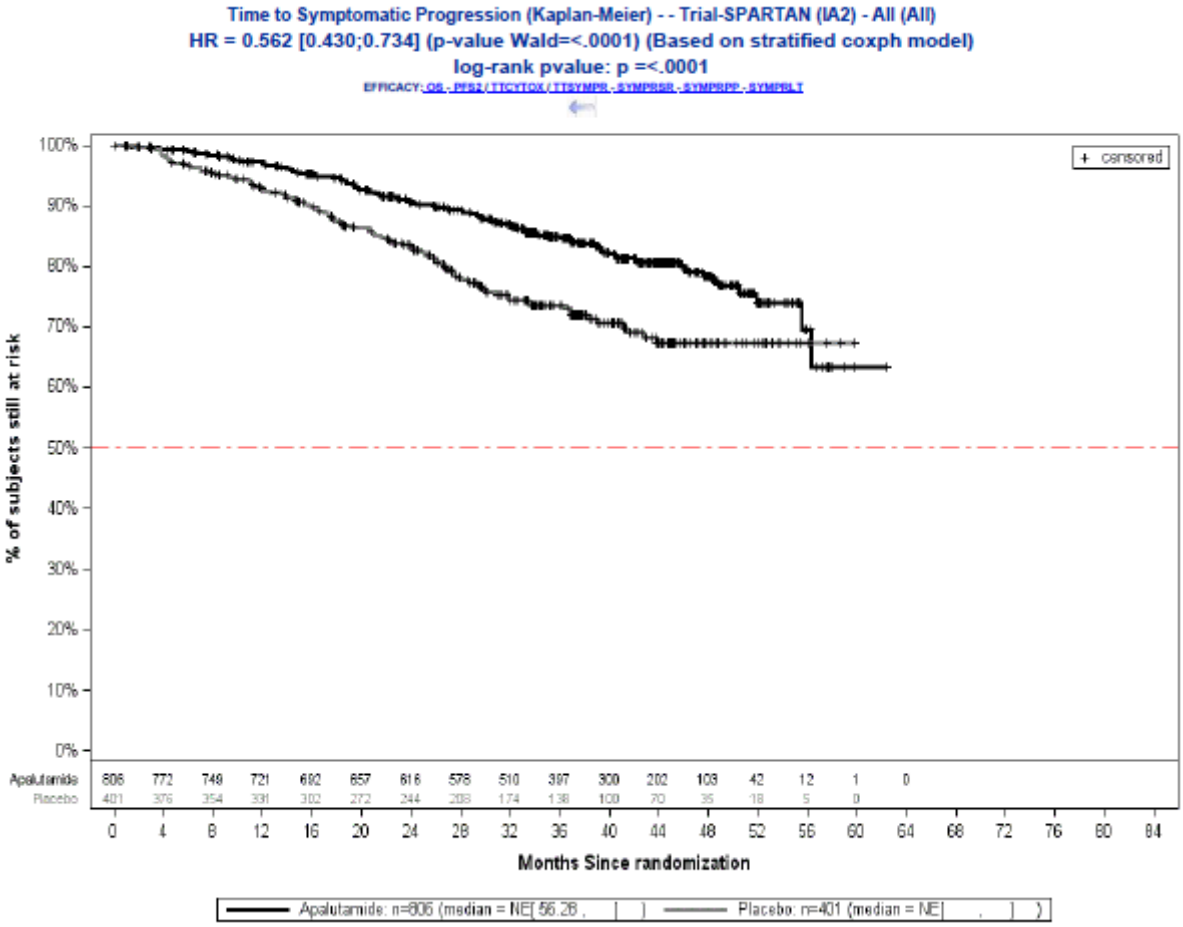

Figure 2: Kaplan-Meier curves for "symptomatic progression" – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (data cut-off: 1 February 2019)

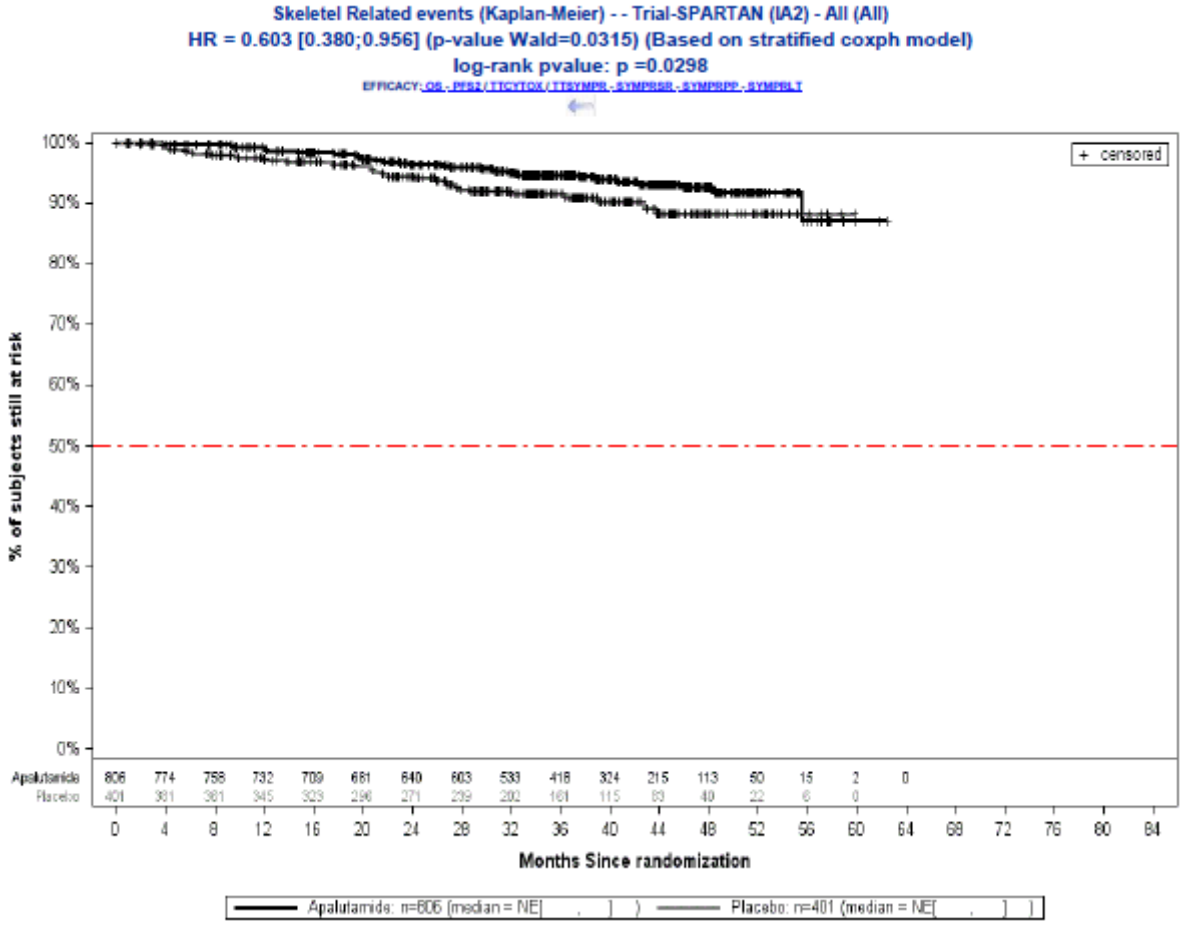

Figure 3: Kaplan-Meier curves for “skeletal-related events” – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (data cut-off: 1 February 2019)

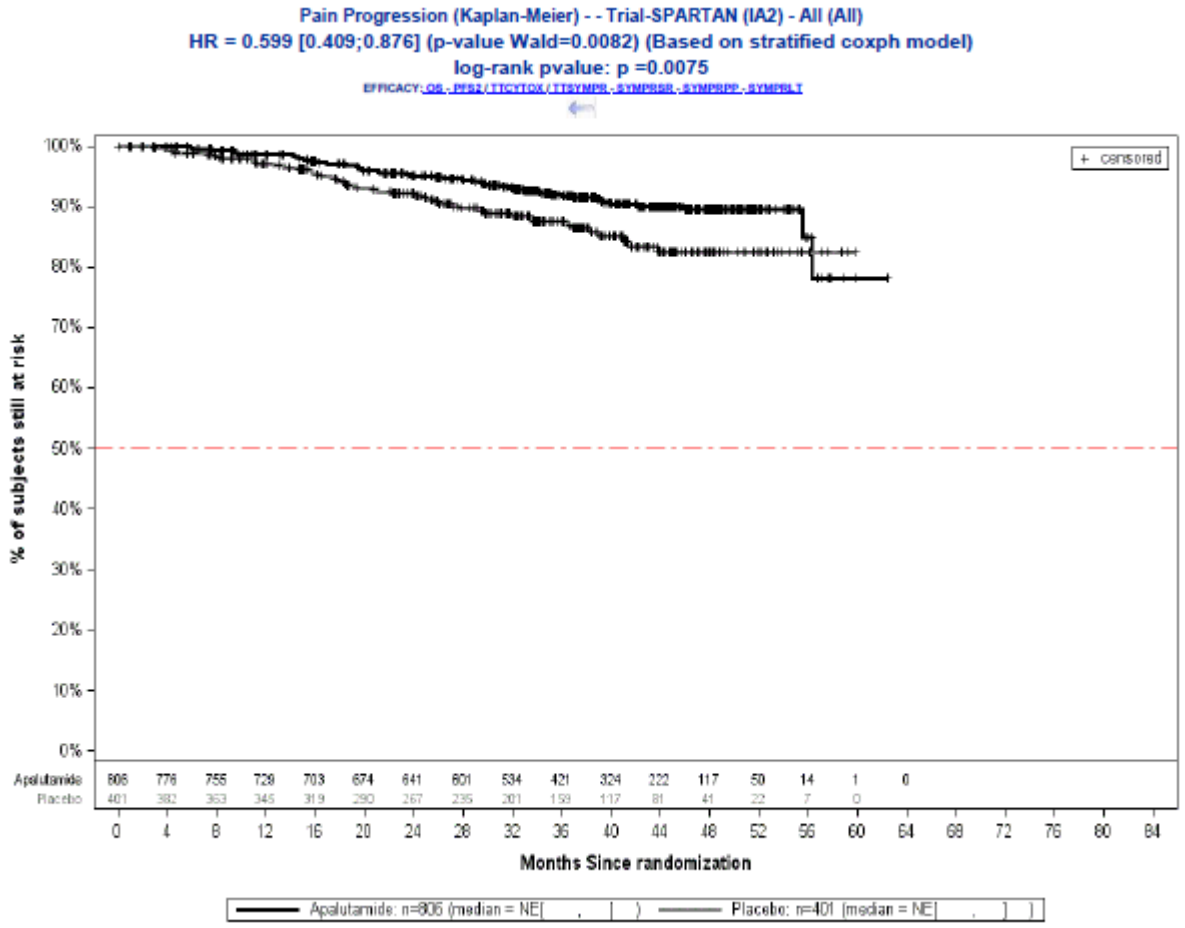

Figure 4: Kaplan-Meier curves for “pain progression” or “deterioration of disease-related symptoms requiring the initiation of a new systemic anticancer therapy” – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (data cut-off: 1 February 2019)

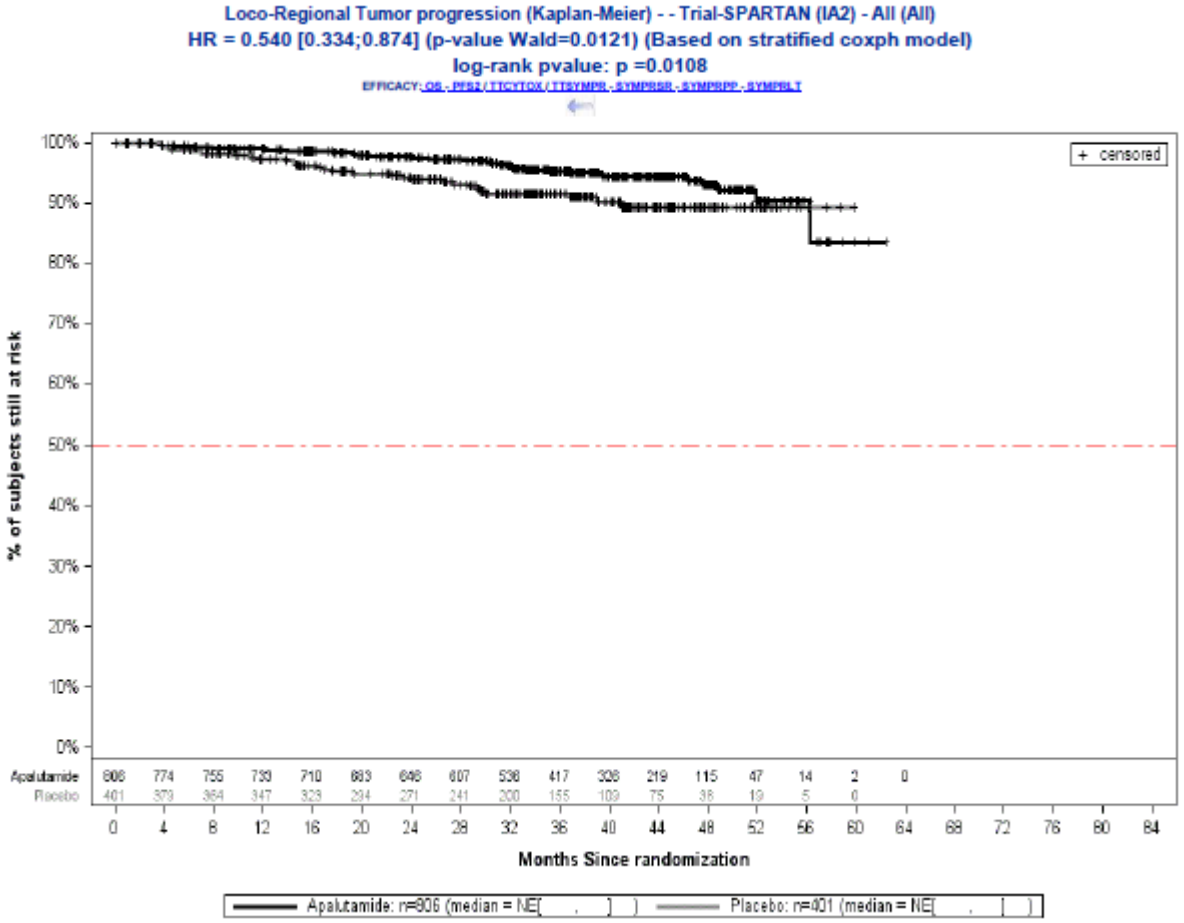

Figure 5: Kaplan-Meier curves for "clinically significant symptoms due to locoregional tumour progression requiring surgical intervention or radiotherapy" – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (data cut-off: 1 February 2019)

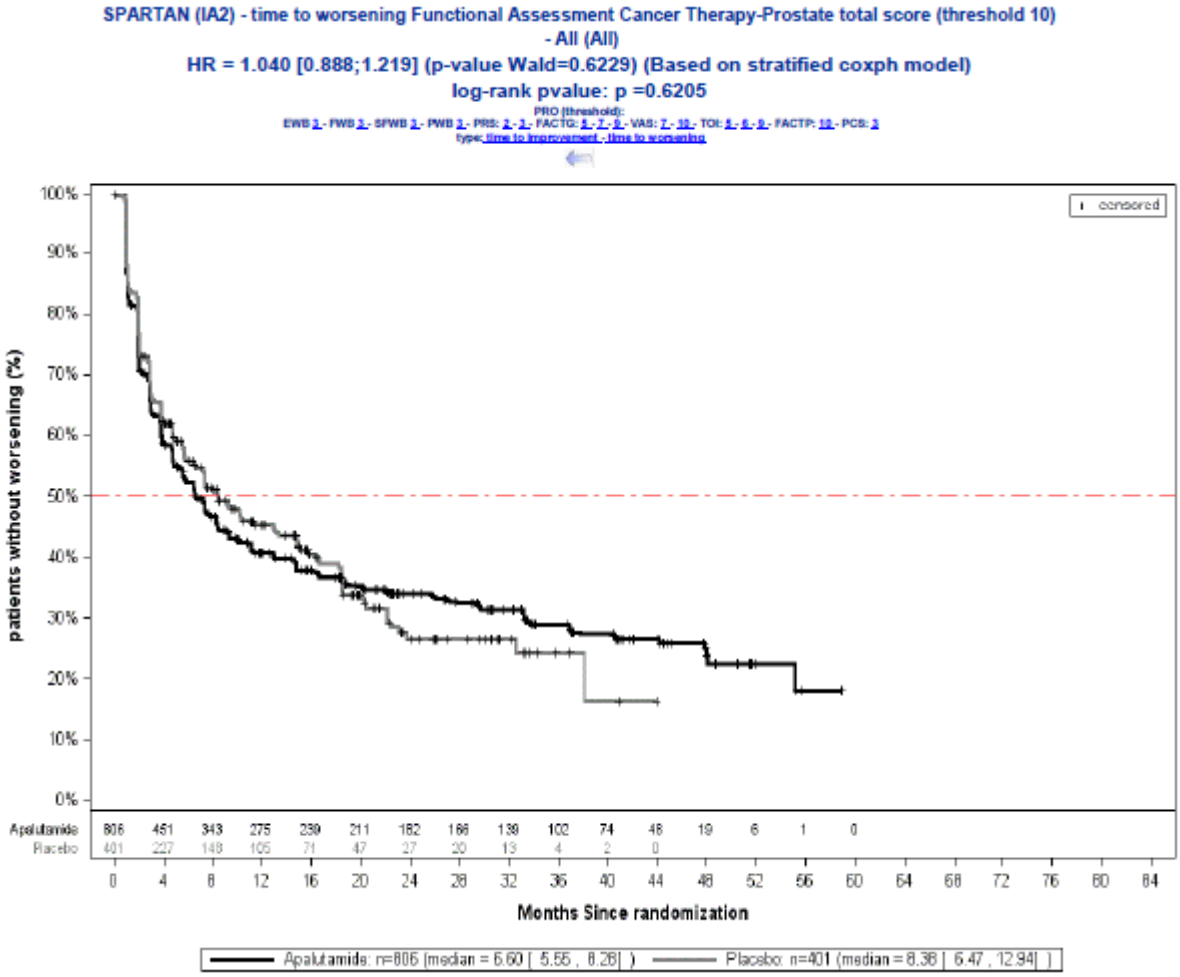

Figure 6: Kaplan-Meier curves for "health-related quality of life (FACT-P total score)"; "time to deterioration" – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (data cut-off: 1 February 2019)

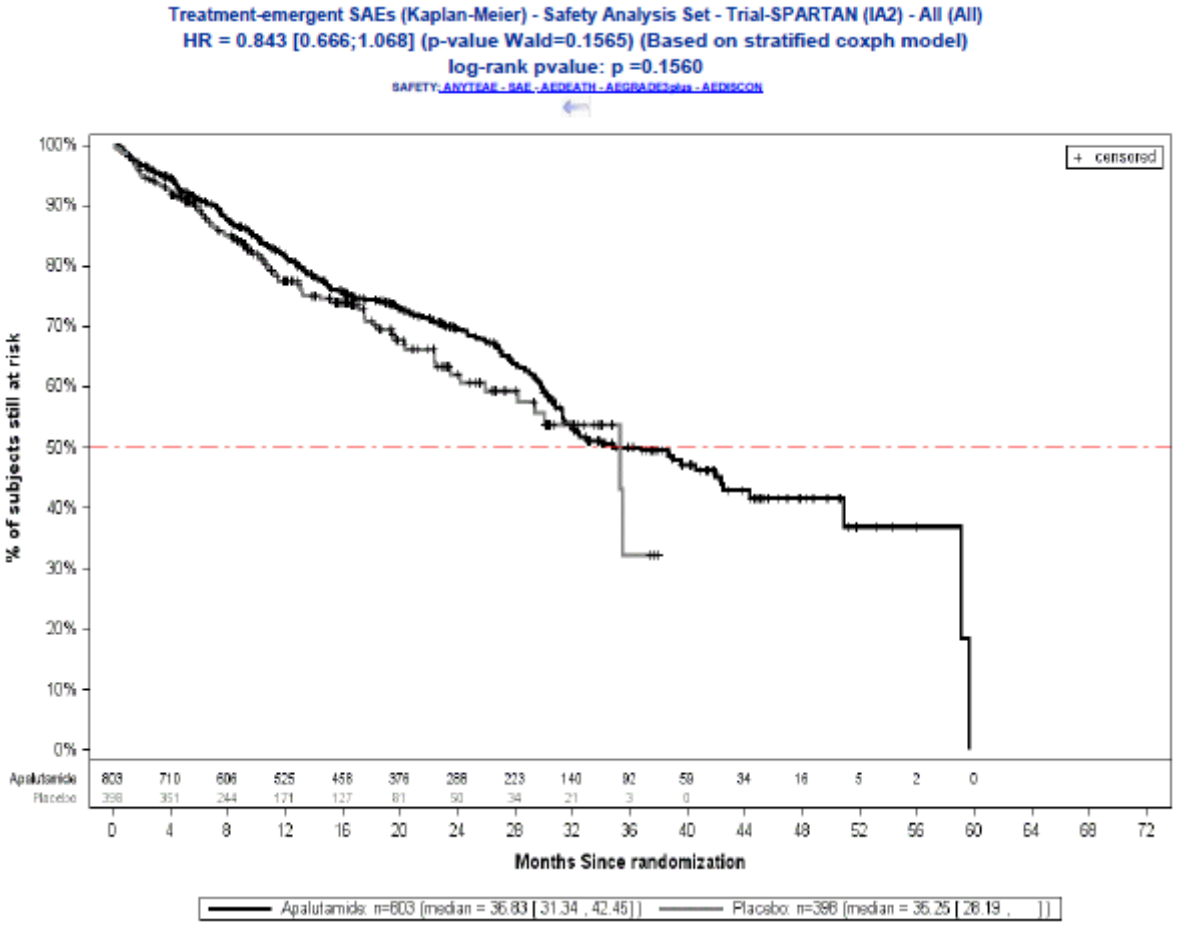

Figure 7: Kaplan-Meier curves for “SAEs including fatal events” – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (data cut-off: 1 February 2019)

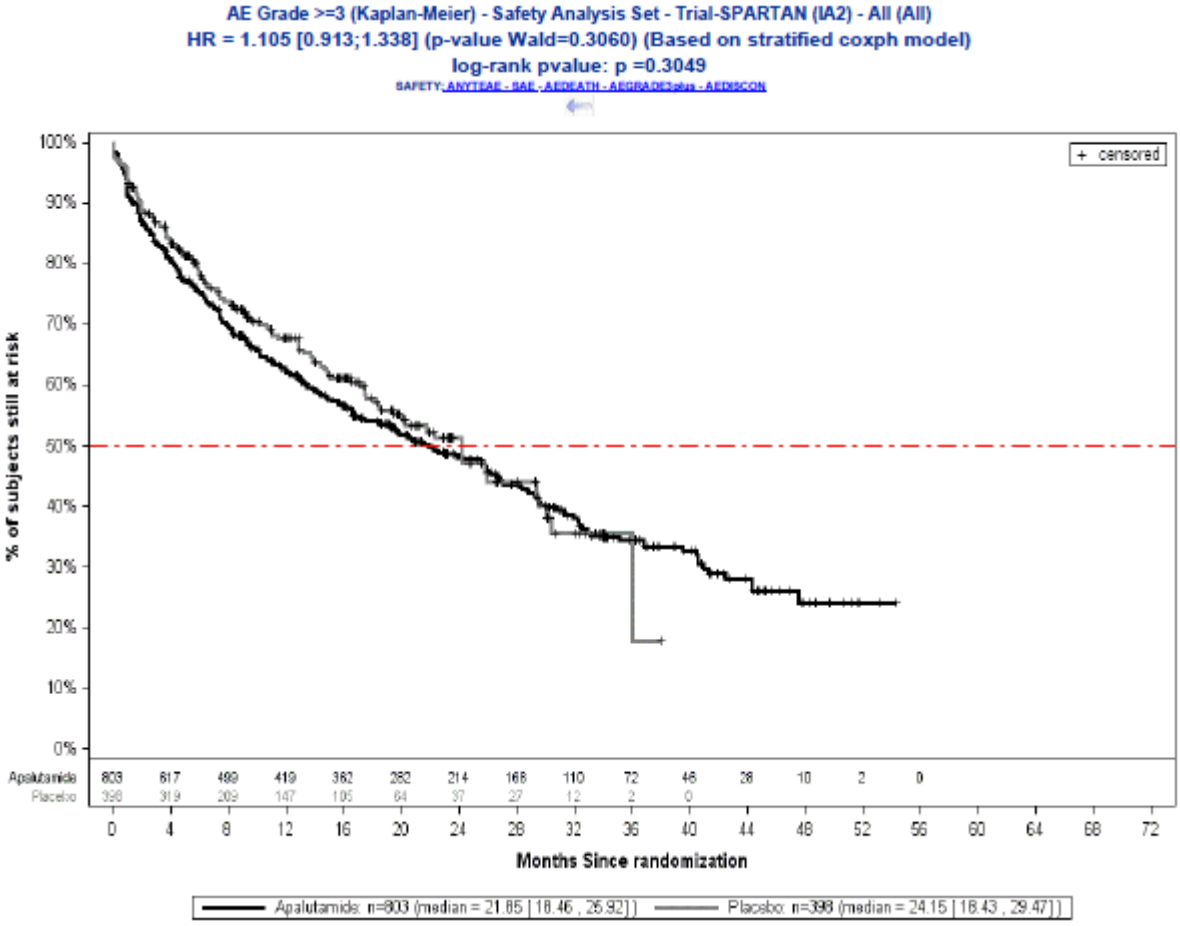

Figure 8: Kaplan-Meier curves for "severe AEs (CTCAE grade ≥ 3)" – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (data cut-off: 1 February 2019)

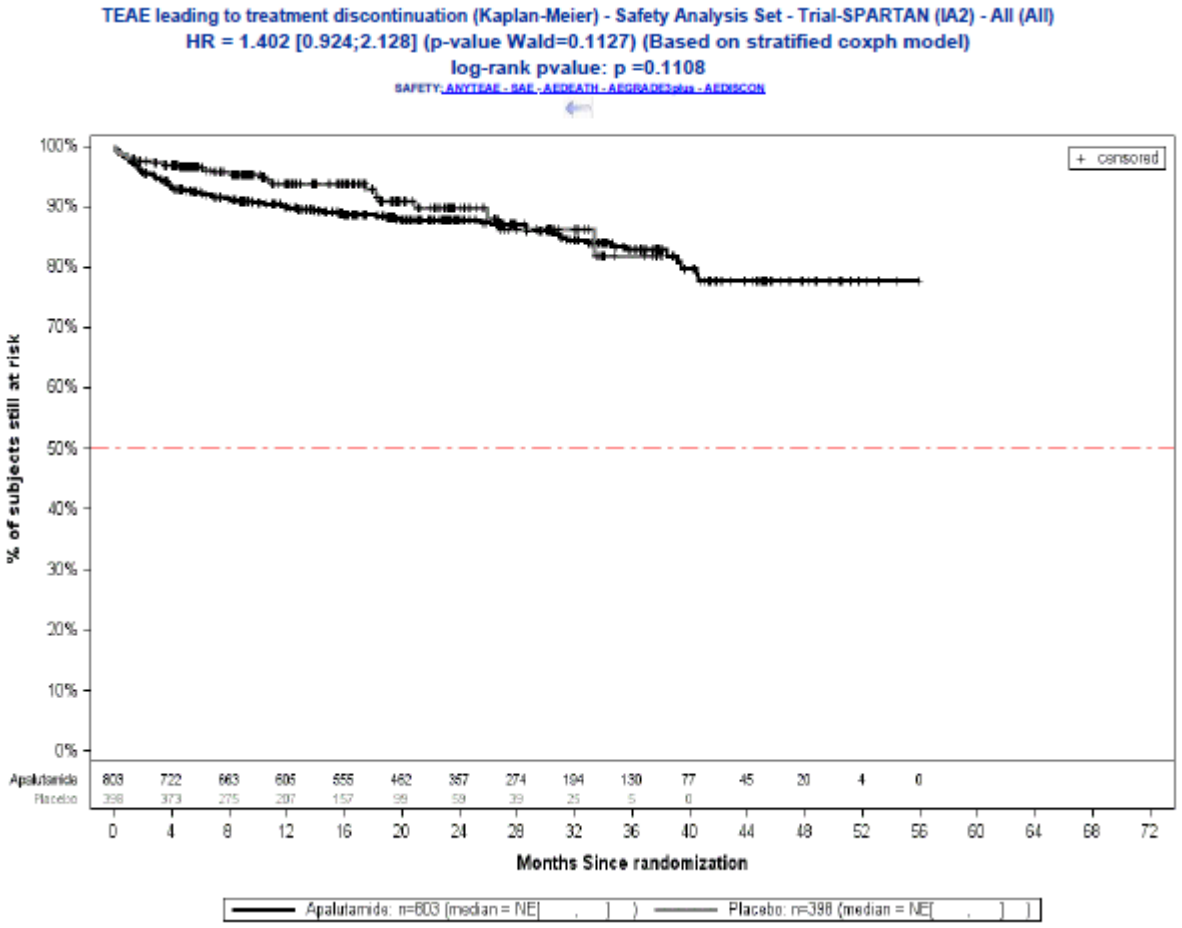

Figure 9: Kaplan-Meier curves for "discontinuation due to AEs" – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (data cut-off: 1 February 2019)

Appendix B – Kaplan-Meier curves on the outcome "SAEs" (data cut-off: 19 May 2017)

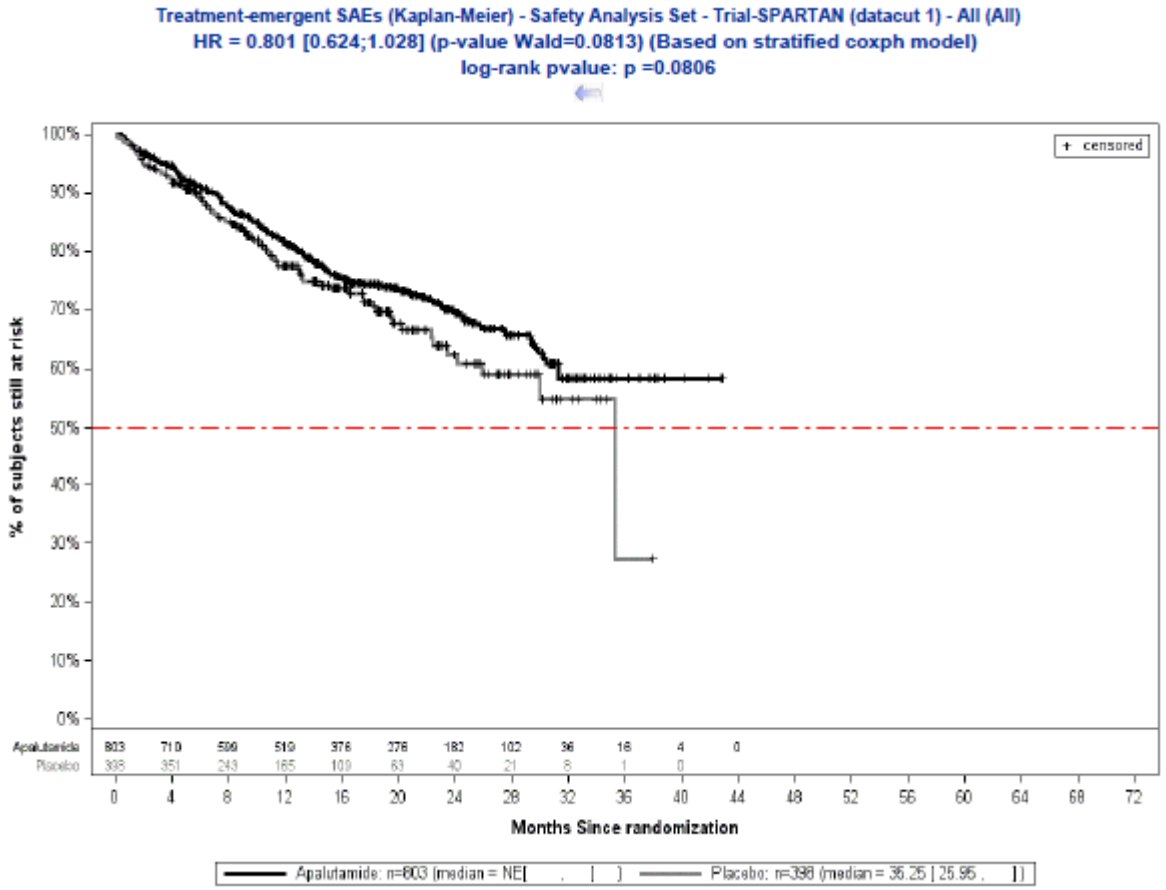

Figure 10: Kaplan-Meier curves for "SAEs including fatal events" – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (data cut-off: 19 May 2017)

Appendix C – Further results on EQ-5D VAS

Table 7: Results (morbidity - further results on outcome EQ-5D VAS) – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (data cut-off: 19 May 2017 and 1 February 2019)

Study Outcome category	Apalutamide + ADT		Placebo + ADT		Apalutamide + ADT vs. placebo + ADT
Outcome Data cut-off	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
SPARTAN					
Morbidity					
Health status (EQ-5D VAS, time to deterioration[b])					
Data cut-off: 19 May 2017					
7 points	806	10.02 [7.43; 14.85] 432 (53.6)	401	11.30 [6.47; 18.50] 198 (49.4)	0.96 [0.81; 1.14]; 0.618
10 points	806	14.69 [9.96; 23.95] 408 (50.6)	401	14.85 [9.27; 18.60] 188 (46.9)	0.93 [0.78; 1.11]; 0.428
Data cut-off: 1 February 2019					
7 points	806	10.02 [7.43; 15.05] 463 (57.4)	401	11.30 [6.47; 18.53] 201 (50.1)	0.95 [0.80; 1.13]; 0.581
10 points	806	14.75 [9.96; 25.79] 439 (54.5)	401	15.70 [9.27; 22.11] 191 (47.6)	0.93 [0.78; 1.10]; 0.391

a: HR, CI and p-value: Cox proportional hazards model; stratified by PSADT (≤ 6 months vs. > 6 months), use of bone-preserving substances (yes vs. no), presence of locoregional disease (N0 vs. N1).
b: Deterioration means decrease in score by the respective MID.

ADT: androgen deprivation therapy; CI: confidence interval; EQ-5D: European Quality of Life5 Dimensions; HR: hazard ratio; MID: minimally important difference; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculable; PSADT: prostata specific antigen doubling time; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

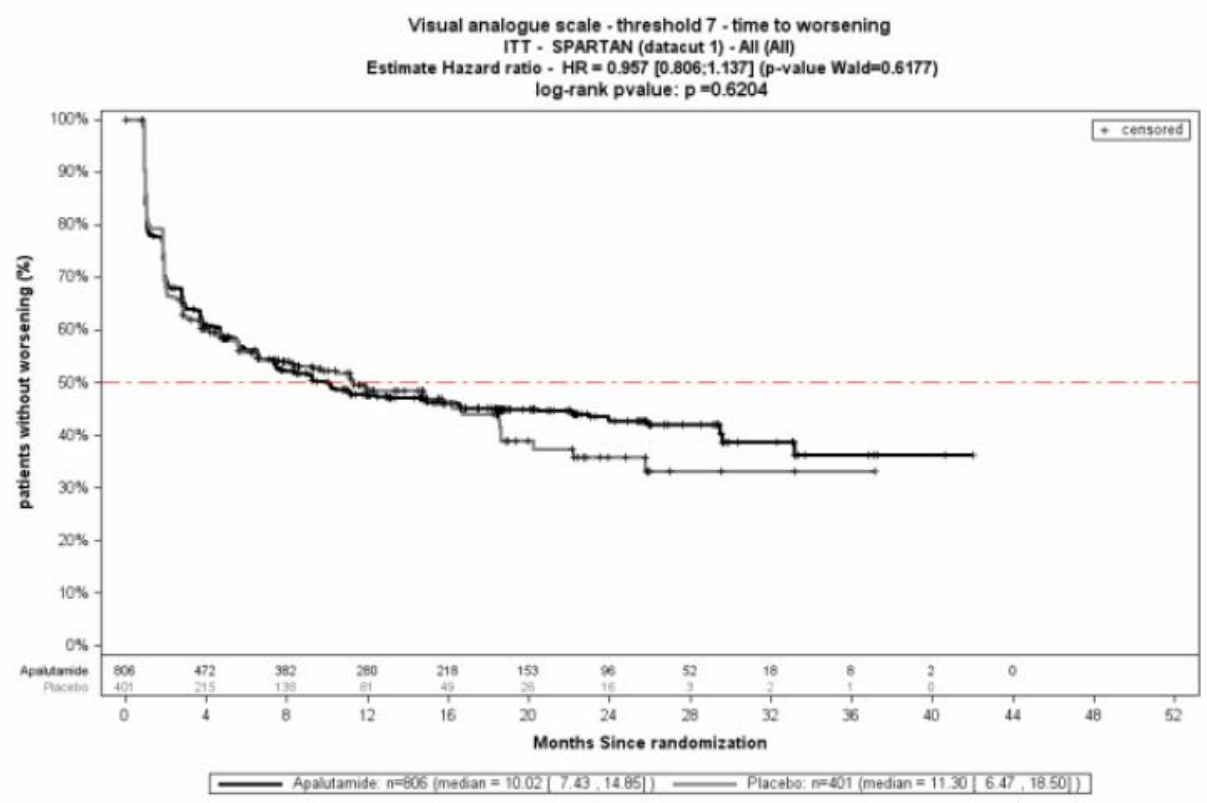

Figure 11: Kaplan-Meier curves for further results on outcome "EQ-5D VAS (time to deterioration by 7 points) – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (data cut-off: 19 May 2017)

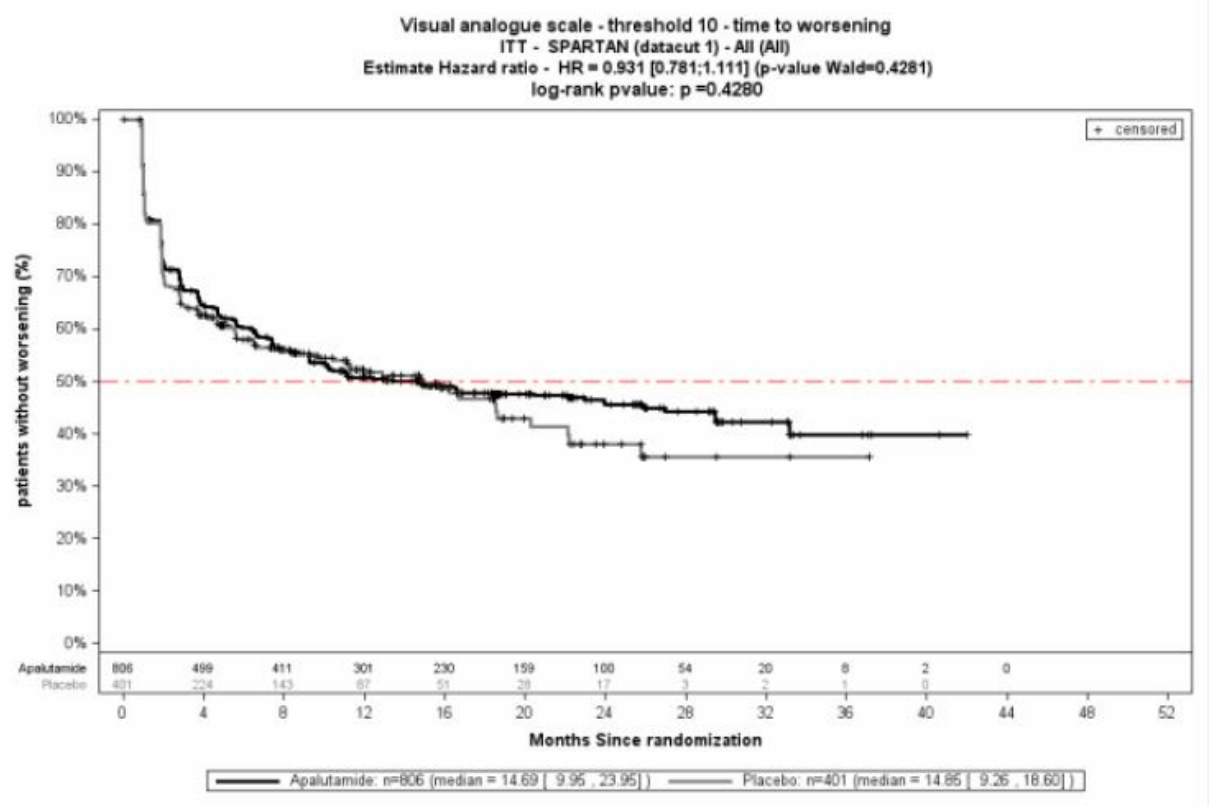

Figure 12: Kaplan-Meier curves for further results on outcome "EQ-5D VAS (time to deterioration by 10 points)" – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (data cut-off: 19 May 2017)

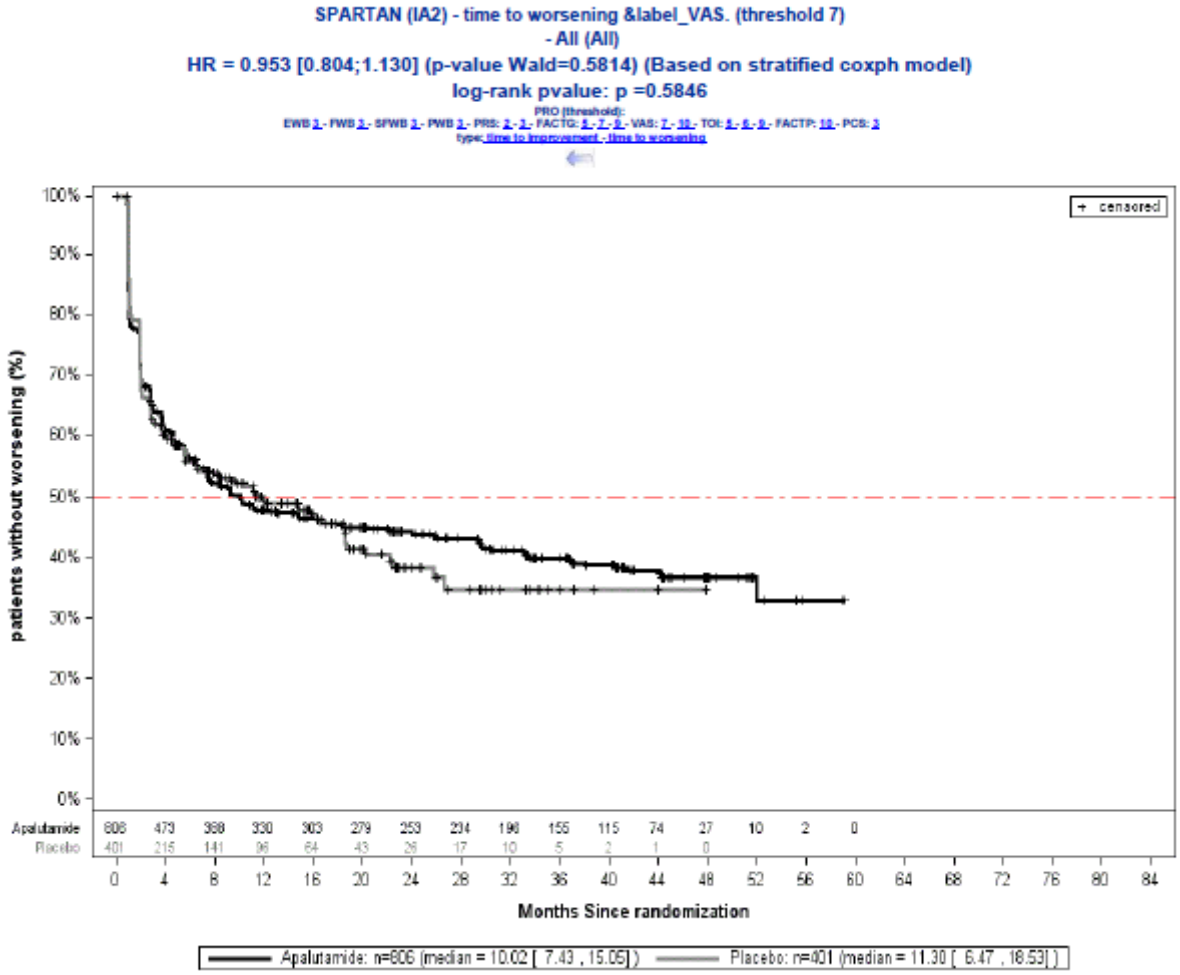

Figure 13: Kaplan-Meier curves for further results on outcome "EQ-5D VAS (time to deterioration by 7 points) – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (data cut-off: 1 February 2019)

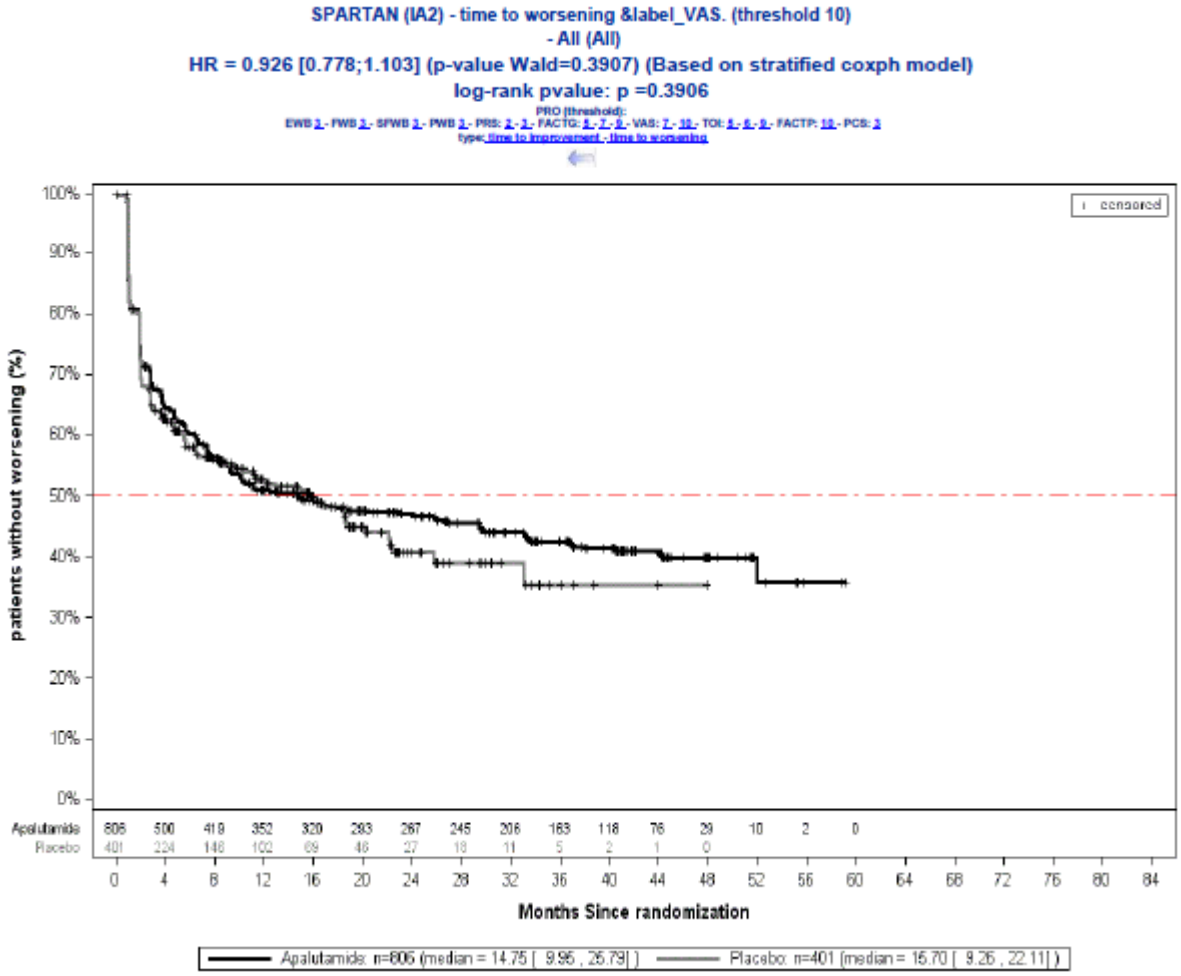

Figure 14: Kaplan-Meier curves for further results on outcome "EQ-5D VAS (time to deterioration by 10 points) – RCT, direct comparison: apalutamide + ADT vs. placebo + ADT (data cut-off: 1 February 2019)