IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A18-26

Abiraterone acetate (prostate cancer) –

Addendum to Commission A17-64[1]

Addendum

Commission: A18-26
Version: 1.0
Status: 11 May 2018

[1] Translation of addendum A18-26 *Abirateronacetat (Prostatakarzinom) – Addendum zum Auftrag A17-64* (Version 1.0; Status: 11 May 2018). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Abiraterone acetate (prostate cancer) – Addendum to Commission A17-64

Commissioning agency:
Federal Joint Committee

Commission awarded on:
25 April 2018

Internal Commission No.:
A18-26

Address of publisher:
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Keywords: abiraterone acetate, prednisone, prednisolone, androgen deprivation therapy, prostatic neoplasms, benefit assessment, NCT01715285, NCT00268476

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ADT	androgen deprivation therapy
AE	adverse event
BFI	Brief Fatigue Inventory
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
mHSPC	high risk metastatic hormone sensitive prostate cancer
P	prednisone/prednisolone
PT	Preferred Term
SAE	serious adverse event
SMQ	Standardized MedDRA Query
SOC	System Organ Class

1 Background

On 25 April 2018, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A17-64 (Abiraterone acetate – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") presented results of the studies LATITUDE and STAMPEDE for the assessment of the added benefit of abiraterone acetate (hereinafter referred to as "abiraterone") in comparison with the appropriate comparator therapy (ACT) in patients with newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC).

With its written comment on the dossier assessment [3] and after the oral hearing, the company submitted further analyses [4] on the LATITUDE study sponsored by the company.

The G-BA commissioned IQWiG with the assessment of the analysis on the outcome "fatigue" (measured with the Brief Fatigue Inventory [BFI]) and of the supplementary analyses from the category of side effects presented by the company.

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 Assessment

2.1 Assessment of the analyses subsequently submitted on the outcome "fatigue" (measured with the BFI)

The LATITUDE study recorded the fatigue experienced by the patients with the BFI questionnaire. The BFI comprises 9 Items, which are rated on a 0 to 10 scale with higher scores indicating more severe symptoms.

For benefit assessment A17-64, the company derived the added benefit on the basis of worst fatigue (BFI Item 3) and fatigue interference (BFI Items 4 a–f). The company had chosen event time analyses with the response criteria of time to deterioration by at least 2 (BFI Item 3) or 1.5 points (BFI Items 4 a–f) as type of analysis for the derivation of the added benefit. In addition to the event time analyses, the company had presented analyses using mean differences. The response criteria chosen by the company for the time to deterioration by at least 2 (BFI Item 3) or 1.5 points (BFI Items 4 a–f) were not used in the benefit assessment. This is justified in dossier assessment A17-64. The mean differences were considered for the benefit assessment. They showed no relevant difference between abiraterone and the comparator group.

With its comment, the company subsequently submitted responder analyses on the operationalizations "time to deterioration by 1 point" to "time to deterioration by 10 points", including all points in between (in whole-numbered intervals), for the outcomes of worst fatigue (BFI Item 3) and fatigue interference (BFI Item 4 a–f). These analyses [3] of responder analyses with a comprehensive range of response criteria subsequently submitted by the company do not replace a substantiated response criterion.

There was a particular data constellation in the present case, however. Across a wide range of threshold values investigated, the responder analyses presented by the company showed consistent effects (or directions of effect) in favour of abiraterone for the outcome "worst fatigue" (BFI Item 3) [3].

In accordance with the BFI validation study by Mendoza 1999 [5], fatigue severity in cancer patients can be classified as "mild", "moderate" and "severe" for worst fatigue (Item 3) of this instrument. According to this classification, a score of 7 to 10 points indicates severe fatigue, and a score of about 3 to 6 indicates moderate fatigue. Hence, using the response criterion "deterioration by ≥ 3 points" would be equivalent to a patient's deterioration by 1 severity grade. Correspondingly, using the response criterion "deterioration by ≥ 6 points" corresponds to deterioration by 2 severity grades. Since both response criteria mentioned showed a statistically significant result in favour of abiraterone for the outcome "worst fatigue" (Item 3), in the present data constellation, these responder analyses can be interpreted jointly with sufficient certainty.

This does not apply to the outcome "fatigue interference" (Item 4a–f) in the same way because, in accordance with Mendoza 1999, threshold values for the classification into severity grades cannot be derived with the same clarity. In addition, the responder analyses on this outcome presented by the company showed no statistically significant result in higher threshold values (e.g. ≥ 6 points).

In summary, the analyses on worst fatigue (Item 3) "deterioration by ≥ 3 points" and "deterioration by ≥ 6 points" were used for the present benefit assessment.

Risk of bias

For the outcome "worst fatigue" (BFI Item 3), the observation period of the survival time analyses was driven by the disease progression. Due to a possible association between disease progression and this outcome, there were probably censorings, which were informative for the analysis. With a ratio of the treatment period of the androgen deprivation therapy (ADT) arm versus the abiraterone-prednisone/prednisolone (P)-ADT arm of 60%, informative censoring to an important degree is possible. The assumption of the Cox proportional hazards model that the censorings were non-informative censorings is potentially violated. The risk of bias of this outcome was therefore rated as high.

Results

The results on the responder analyses on the outcome "fatigue", measured with the BFI, are presented in Table 1.

Table 1: Results (morbidity, time to event) – RCT, direct comparison: abiraterone-P-ADT vs. ADT

Study Outcome category Outcome	Abiraterone-P-ADT N	Median time to event in months [95% CI] Patients with event n (%[b])	ADT[a] N	Median time to event in months [95% CI] Patients with event n (%[b])	Abiraterone-P-ADT vs. ADT HR [95% CI]; p-value[c]
LATITUDE					
Morbidity					
Time to deterioration of worst fatigue (BFI, Item 3) by					
≥ 3 points	597	NA 96 (16.1)	602	NA 133 (22.1)	0.59 [0.45; 0.77]; < 0.001
≥ 6 points	597	NA 21 (3.5)	602	NA 36 (6.0)	0.50 [0.29; 0.86]; 0.012

a: ADT + placebo for abiraterone and prednisone.
b: Institute's calculation.
c: Cox model stratified by visceral metastasis (yes/no) and ECOG Performance Status (0/1 vs. 2).
ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; NA: not achieved; ND: no data; RCT: randomized controlled trial; vs.: versus

The LATITUDE study showed a statistically significant difference in favour of abiraterone-P-ADT versus ADT for the outcome "worst fatigue", measured with BFI Item 3, both when using the response criterion "deterioration by ≥ 3 points" and when using the response criterion "deterioration by ≥ 6 points". There was an outcome-specific high risk of bias for this outcome. This resulted in a hint of an added benefit of abiraterone-P-ADT in comparison with ADT for worst fatigue.

2.2 Assessment of the analyses on the category of side effects subsequently submitted

Assessment of the company's approach for the presentation of AEs at SOC level in the dossier

With its dossier, the company had presented survival time analyses for adverse events (AEs) with threshold values of 5% for any AE, of 1% for severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3–4), and occurrence in at least 2 patients for serious AEs (SAEs) for the LATITUDE study. According to information provided by the company, the respective threshold values were used at Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) level. A corresponding System Organ Class (SOC) level was only generated if an individual PT within the SOC exceeded the threshold value.

This approach was inadequate. As a result of this approach, SOCs are not presented if all subordinate PTs are below the predefined threshold value. Particularly in cases where many PTs of the same SOC that are associated with regard to content are below the threshold value, there is a risk that an effect in a SOC that is a meaningful combination of these PTs is overlooked.

The analyses subsequently submitted by the company after the oral hearing used no threshold values (neither at PT nor at SOC level); hence, the SOCs on AEs irrespective of their severity grade, on severe AEs and on SAEs could be considered for the choice of specific AEs.

Specific AEs for the benefit assessment were chosen using the events that occurred in the relevant studies on the basis of frequency and differences between the treatment arms and under consideration of the patient relevance. In addition, specific AEs of particular importance for the disease or for the drugs used in the study could be chosen.

Based on this method, the company's subsequent submission based on SOCs did not result in the identification of further specific AEs in comparison with benefit assessment A17-64.

Results subsequently submitted on the outcomes "cardiac failure" and "ischaemic heart disease"

The AEs "cardiac failure" and "ischaemic heart disease" were chosen in benefit assessment A17-64 because they are known side effects of abiraterone. As shown in benefit assessment A17-64, these two AEs were operationalized in the LATITUDE study as 2 of 4 subgroups of the AE "cardiac disorders". The 2 remaining subgroups are arrhythmias and other cardiac disorders.

According to the information provided in the clinical study report (CSR), the PTs for the subgroups were chosen a priori using modified Standardized MedDRA Queries (SMQs). The study documents refer to the abiraterone studies COU-AA-301 and COU-AA-302 [6,7]. In addition, the statistical analysis plan on the LATITUDE study presents the PTs included in both (modified) SMQs "cardiac failure" and "ischaemic heart disease". These differed in their composition from the modified SMQs mentioned in the studies COU-AA-301 and COU-AA-302, however. Irrespective of these inconsistencies, it is not clear which criteria were used for the creation of the modified SMQs. Due to the uncertainty of the events included in both outcomes, the results on the SOC "cardiac disorders" (severe AEs [CTCAE grade 3–4]) were used for the present addendum, grouping both aspects "cardiac failure" and "ischaemic heart disease" (see the following Table 2). The results on SAEs of the SOC "cardiac disorders" are presented as supplementary information.

Table 2: Results (side effects) – RCT, direct comparison: abiraterone-P-ADT vs. ADT

Study **Outcome category**	**Abiraterone-P-ADT**		**ADT[a]**		**Abiraterone-P-ADT vs. ADT**
Outcome	**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**
LATITUDE					
Side effects					
AEs with CTCAE grade 3–4					
Cardiac disorders	597	ND 18 (3.0)	602	ND 5 (0.8)	2.82 [1.04; 7.65]; 0.041
SAEs (supplementary information)					
Cardiac disorders	597	ND 19 (3.2)	602	ND 2 (0.3)	7.33 [1.70; 31.63]; 0.008

a: ADT + placebo for abiraterone and prednisone.

ADT: androgen deprivation therapy; AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; P: prednisone/prednisolone; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The LATITUDE study showed a statistically significant difference to the disadvantage of abiraterone-P-ADT in comparison with ADT for the outcome "severe cardiac disorders" (CTCAE grade 3–4). There was an outcome-specific high risk of bias for this outcome, as for all AE outcomes (see [1]). This resulted in a hint of greater harm of minor extent for abiraterone-P-ADT in comparison with ADT.

Effects of the data on AEs subsequently submitted on the overall conclusion on the added benefit

The extent of the added benefit at outcome level was estimated on the basis of benefit assessment A17-64 and under consideration of the responder analyses presented by the company with the comment as well as the analyses on AEs subsequently submitted (see Table 3).

Table 3: Extent of added benefit at outcome level: abiraterone-P-ADT vs. ADT

Outcome category **Outcome**	**Abiraterone-P-ADT vs. ADT[a]** **Median time to event (months) or proportion of events (%) or MD** **Effect estimate [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Mortality		
Overall survival	NA vs. 34.7–48 HR 0.62 [0.53; 0.71]; p < 0.001 probability: "proof"	Outcome category: "mortality" CI_u < 0.85 Added benefit, extent: "major"
Morbidity		
Symptomatic local disease progression	NA vs. NA HR 0.67 [0.42; 1.08]; p = 0.101	Lesser benefit/added benefit not proven
Skeletal-related events[d]	NA vs. NA heterogeneous results; there was a statistically significant effect in favour of abiraterone in both studies probability: "indication"	Outcome category: serious/severe symptoms/late complications added benefit, extent: "non-quantifiable"
Symptoms (recorded with the EORTC QLQ-C30 and PR25)[e]	Recorded, but not reported	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)		
LATITUDE: time to worsening, response criterion 7 points	9.2 vs. 5.6 HR: 0.81 [0.70; 0.94][f]; p = 0.004	Lesser benefit/added benefit not proven
LATITUDE: time to worsening, response criterion 10 points	12.9 vs. 8.3 HR: 0.83 [0.72; 0.97][f]; p = 0.015	
STAMPEDE	Recorded, but not reported	
Pain		
Worst Pain (BPI-SF Item 3), time to deterioration, response criterion 2 points	NA vs. NA HR 0.63 [0.52; 0.77]; p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.8 added benefit, extent: "considerable"
EORTC QLQ-C30 pain symptom scale	Recorded, but not reported	Lesser benefit/added benefit not proven
Pain interference (BPI-SF Items 9 a–g)	−0.14 vs. 0.19[g] MD −0.34 [−0.49; −0.18]; p < 0.001 Hedges' g: −0.25 [−0.36; −0.13][h]	Lesser benefit/added benefit not proven

(continued)

Table 3: Extent of added benefit at outcome level: abiraterone-P-ADT vs. ADT (continued)

Outcome category **Outcome**	**Abiraterone-P-ADT vs. ADT[a]** **Median time to event (months) or proportion of events (%) or MD** **Effect estimate [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Fatigue		
Worst fatigue (BFI Item 3), time to deterioration	Response criterion 3 points NA vs. NA HR 0.59 [0.45; 0.77]; p < 0.001 Response criterion 6 points NA vs. NA HR 0.50 [0.29; 0.86]; p = 0.012 probability: "hint"	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.9$ added benefit, extent: "considerable"
EORTC QLQ-C30 fatigue symptom scale	Recorded, but not reported	Lesser benefit/added benefit not proven
Fatigue interference (BFI Items 4 a–f)	−0.12 vs. 0.16[g] MD −0.28 [−0.43; −0.12]; p < 0.001 Hedges' g: −0.21 [−0.33; −0.09][h]	Lesser benefit/added benefit not proven
Health-related quality of life		
Recorded with FACT-P, total score, time to deterioration, response criterion 10 points	12.9 vs. 8.3 HR 0.85 [0.74; 0.99]; p = 0.035 Probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit, extent: "minor"
Recorded with EORTC QLQ-C30[i]	Recorded, but not reported	Lesser benefit/added benefit not proven
Side effects		
SAEs	NA vs. NA HR 0.85 [0.68; 1.07]; p = 0.169	Greater/lesser harm not proven
Severe AEs (CTCAE grade 3–4)	13.9 vs. 20.2 HR 1.26 [1.08; 1.48]; HR: 0.79 [0.68; 0.93][j]; p = 0.003 Probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: "minor"
Discontinuation due to AEs	12.2% vs. 10.1% RR 1.21 [0.88; 1.66]; p = 0.272	Greater/lesser harm not proven

(continued)

Table 3: Extent of added benefit at outcome level: abiraterone-P-ADT vs. ADT (continued)

Outcome category **Outcome**	**Abiraterone-P-ADT vs. ADT[a]** **Median time to event (months) or proportion of events (%) or MD** **Effect estimate [95% CI]; p-value** **Probability[b]**	**Derivation of extent[c]**
Specific AEs		
Fluid retention/oedema	NA vs. NA HR 0.96 [0.69; 1.33]; p = 0.783	Greater/lesser harm not proven
Cardiac disorders (CTCAE grade 3–4)[k]	ND vs. ND HR 2.82 [1.04; 7.65] HR 0.35 [0.13; 0.96][j]; p = 0.041 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Hypokalaemia (CTCAE grade 3–4)	NA vs. NA HR 6.32 [3.02; 13.21]; HR 0.16 [0.08; 0.33][j]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% greater harm, extent: "major"
Alanine aminotransferase (ALT) increased (CTCAE grade 3–4)	NA vs. NA HR 3.99 [1.84; 8.65]; HR 0.25 [0.12; 0.54][j]; p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% greater harm, extent: "major"
Aspartate aminotransferase (AST) increased (CTCAE grade 3–4)	NA vs. NA HR 2.72 [1.27; 5.80]; HR 0.37 [0.17; 0.79][j]; p = 0.010 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"

(continued)

Table 3: Extent of added benefit at outcome level: abiraterone-P-ADT vs. ADT (continued)

a: LATITUDE study: ADT + placebo for abiraterone and prednisone; STAMPEDE study: ADT.
b: Probability given if statistically significant differences are present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: No common effect estimate can be provided due to heterogeneous data.
e: The EORTC QLQ-C30 contains 8 relevant morbidity outcomes, 4 of which are symptom scales. The 2 symptom scales of pain and fatigue are grouped separately under the category of pain and fatigue. In addition to the EORTC QLQ-C30, the additional module QLQ-PR25, which contains 4 further prostate cancer-specific symptom scales and 2 functional scales, was recorded in the STAMPEDE study.
f: The extent of the effect in this non-serious/non-severe outcome is no more than marginal.
g: Mean changes per treatment arm in the included study.
h: If the CI of Hedges' g is fully outside the irrelevance range [−0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
i: The outcome category health-related quality of life of the EORTC QLQ-C30 contains 5 functional scales and one scale on global health status.
j: Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
k: The results of the SOC "cardiac disorders" (CTCAE grade 3–4) are used as an approximation to the specific AEs "cardiac failure" and "ischaemic heart disease".

ADT: androgen deprivation therapy; AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-PR25: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; MD: mean difference; NA: not achieved; ND: no data; P: prednisone/prednisolone; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Under consideration of the responder analyses presented by the company with the comment and the analyses on AEs subsequently submitted, the positive and negative effects of abiraterone in comparison with the ACT are as presented in the following Table 4.

Table 4: Positive and negative effects from the assessment of abiraterone-P-ADT in comparison with ADT

Positive effects	**Negative effects**
Mortality ▪ Overall survival: proof of an added benefit – extent: “major”	–
Serious/severe symptoms/late complications ▪ skeletal-related events: indication of an added benefit – extent: “non-quantifiable” ▪ Worst fatigue (BFI Item 3): hint of an added benefit – extent: “considerable”	–
Non-serious/non-severe symptoms/late complications ▪ pain: hint of an added benefit – extent “considerable”	–
Health-related quality of life ▪ recorded with FACT-P: hint of a minor added benefit	–
–	Serious/severe side effects ▪ severe AEs (CTCAE grade 3–4): hint of greater harm – extent: “minor” ▪ hypokalaemia (CTCAE grade 3–4): hint of greater harm – extent: “major” ▪ alanine aminotransferase (ALT) increased (CTCAE grade 3–4): hint of greater harm – extent: “major” ▪ aspartate aminotransferase (AST) increased (CTCAE grade 3–4): hint of greater harm – extent “considerable” ▪ cardiac disorders (CTCAE grade 3–4): hint of greater harm – extent: “minor”
Further uncertainties: ▪ In the STAMPEDE study, the patient questionnaires EORTC QLQ-C30 and PR25, as well as EQ-5D-5L, were recorded, but the results were reported neither for the total population nor for the M1 patient population. Hence, there were incomplete data on the outcome categories of morbidity and health-related quality of life. In addition, there were no systematic analyses on AEs for the M1 patient population of the STAMPEDE study.	
ADT: androgen deprivation therapy; AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EORTC QLQ-PR25: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Prostate 25; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; FACT-P: Functional Assessment of Cancer Therapy-Prostate; P: prednisone/prednisolone	

The data subsequently submitted resulted in changes both on the side of positive and on the side of negative effects. Overall, these did not change the conclusion on the added benefit drawn in benefit assessment A17-64.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure did not change the conclusion on the added benefit of abiraterone from dossier assessment A17-64.

The following Table 5 shows the result of the benefit assessment of abiraterone under consideration of dossier assessment A17-64 and the present addendum.

Table 5: Abiraterone – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients with newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC)	▪ conventional androgen deprivation therapy (ADT)[b] ▪ if applicable, in combination with non-steroidal anti-androgens (flutamide or bicalutamide)	Proof of considerable added benefit[c]
a: Presentation of the respective ACT specified by the G-BA. b: Surgical castration or medical castration using treatment with LH-RH analogues or GnRH antagonists. c: Patients with brain metastasis or an ECOG/WHO Performance Status of > 2 were not investigated in the studies LATITUDE and STAMPEDE. ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; ECOG: Eastern Cooperative Oncology Group; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; LH-RH: luteinizing hormone-releasing hormone; mHSPC: metastatic hormone sensitive prostate cancer; WHO: World Health Organization		

The G-BA decides on the added benefit.

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