Niraparib/abiraterone acetate (prostate cancer 1)

Addendum to Project A23-107 (dossier assessment)[1]

ADDENDUM

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Abbreviation	Meaning
BRCA1/2	breast cancer susceptibility gene 1 or 2
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
mCRPC	metastatic castration-resistant prostate cancer
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 26 March 2024, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-107 (Niraparib/abiraterone acetate– Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprised the assessment of the data and analyses for the outcome "symptomatic progression" from the MAGNITUDE study subsequently submitted by the pharmaceutical company (hereinafter referred to as "the company") in the commenting procedure [2] and after the oral hearing [3], taking into account the information in the dossier [4].

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

For the benefit assessment of niraparib/abiraterone acetate in combination with prednisone or prednisolone (hereinafter referred to as niraparib/abiraterone acetate + P) in patients with metastatic castration-resistant prostate cancer (mCRPC) and mutation in the breast cancer susceptibility gene 1 or 2 (BRCA1/2), in whom chemotherapy is not clinically indicated, the double-blind, randomized MAGNITUDE study was used for research question 1 (treatment-naive mCRPC), in which niraparib + abiraterone acetate + P was compared with placebo + abiraterone acetate + P. A detailed description of the MAGNITUDE study and the subpopulation relevant for the benefit assessment can be found in dossier assessment A23-107 [1].

In the MAGNITUDE study, the outcome of symptomatic progression was one of the outcomes assessed. As described in dossier assessment A23-107, “symptomatic progression” is generally a patient-relevant outcome. However, based on the information presented with the dossier, it was not possible to assess whether the outcome is usable in the operationalization chosen by the company (see A23-107 for reasons [1]).

With its comments [2] and following the oral hearing [3], the company presented further data and analyses for the outcome "symptomatic progression", which are assessed below.

2.1 Assessment of the outcome “symptomatic progression”

The outcome of symptomatic progression is a composite outcome, the recording of which was predefined in the MAGNITUDE study. As described in the benefit assessment, however, precise and detailed information on how this composite outcome was recorded and analysed was lacking. For example, for the benefit assessment, it remained unclear

- which events were defined as symptomatic and which events were actually included in the composite outcome,
- whether all events included (in particular for the components "cancer-related morbid events" and "use of other cancer-related procedures") are necessarily patient-relevant and
- how the analysis dealt with the fact that the component "initiation of a new systemic anti-cancer therapy because of cancer pain" was only included in Version 5 of the electronic case report form dated 16 January 2020, and it must therefore be assumed that this component was not recorded in the first year after recruitment.

With the comment, the company presented further information and analyses that partially, albeit not completely, resolve these ambiguities. This is explained below.

Recorded events and sensitivity analysis presented by the company with the comments

To specify which events were recorded in the outcome "symptomatic progression", the company presented a list of the included categories (referred to by the company as "terms") with the comments. Only the component "cancer-related morbid events" is subdivided into more than 1 category. For all other components, the category corresponds to the superordinate component already mentioned in the dossier. It therefore remains unclear which events were actually recorded in this outcome. With regard to the assessment of patient relevance - as described in the benefit assessment - this is particularly relevant for the components "cancer-related morbid events" and "use of other cancer-related procedures".

For the component "cancer-related morbid events", the company provided information on the distribution of events in the categories of spinal cord compression, fractures (symptomatic and/or pathological), urinary tract obstruction, other urinary tract symptoms and acute kidney injury. Patient relevance or comparability of the severity of events is not immediately apparent for all of these events. In the comments, the company addressed this uncertainty with a sensitivity analysis that only considered the events of spinal cord compression or fractures (symptomatic and/or pathological) in this component. All events recorded under “urinary tract obstruction”, “other urinary tract symptoms” or “acute kidney injury” are not included in this analysis. This approach is comprehensible and appropriate. No further information is available for the component "use of other cancer-related procedures".

In addition, the company presents a list of qualifying events for the composite outcome, which are added in footnote "b" in Table 1.

Irrespective of the fact that it is unclear which events were actually considered in the composite outcome, the chosen operationalization, namely the retrospective recording of an intervention (radiotherapy, orthopaedic intervention, systemic cancer therapy) due to symptoms, is insufficient to record the events of symptomatic progression with sufficient sensitivity. This is also not remedied by the 2nd sensitivity analysis presented by the company, which additionally includes the component "initiation of chronic opioid use". As already described in the benefit assessment, even this component does not ensure a comprehensive recording of the events of pain progression. Thus, the sensitivity analysis only records the start of opioid therapy, but not, for example, other supportive, symptom-relieving therapies. To ensure reliable measurement, the symptomatic event should be recorded directly and not indirectly by recording the initiation of treatment. The related consequences are described in the summarizing section below.

Component “initiation of a new systemic anti-cancer therapy because of cancer pain

In the comments, the company states that no patient had started a new systemic anti-cancer therapy before the amended Version 5 of the electronic case report form. This means that the

lack of recording of this component during the first year after recruitment has no consequences.

Component “use of external radiotherapy for skeletal events”

For the component “use of external radiotherapy for skeletal events”, it remains unclear whether palliative radiotherapy was possible without restriction throughout the entire course of the study. In its comments, the company states that concomitant radiotherapy would have been available to all patients at any time during the study. This contrasts with the information provided in the various study protocol versions, according to which radiotherapy was not permitted up to protocol version 2, and then only in individual cases in consultation with the sponsor.

Summary and consequences for the extent of the added benefit

Overall, the outcome can be used for the benefit assessment, taking into account the analysis described by the company as a sensitivity analysis (for the component "cancer-related morbid events"). There are still uncertainties as to which events were recorded in the component "other cancer-related procedures". In addition, the operationalization chosen by the company (retrospective recording of an intervention due to symptoms) is insufficient to record the events of symptomatic progression with sufficient sensitivity. Therefore, the extent of added benefit cannot be quantified for the outcome “symptomatic progression”.

2.1.1 Risk of bias and certainty of conclusions

The risk of bias of the results on the outcome “symptomatic progression” was rated as high. This is due to the fact that a high proportion of events only occurred after a change of treatment (45% according to the company's statement in the oral hearing [3]) and thus at a time when both the patients and the treating persons were possibly no longer blinded. As most of the results were recorded retrospectively, it cannot be ruled out that the decision as to whether an event was categorized as a symptomatic progression event was biased by the knowledge of the study medication received.

Irrespective of this aspect described under the risk of bias, the certainty of conclusions of the study results is reduced due to the uncertainties described in the benefit assessment as to whether chemotherapy was clinically not indicated for all patients in the study population, whether the potentially relatively long duration of homologous recombination repair mutation testing with permitted bridging therapy is transferable to the current health care context and whether adequate concomitant treatment of bone metastases was possible for all patients. Due to this limitation, overall, at most hints, e.g. of an added benefit, can be determined for all outcomes.

2.1.2 Results

The results on the outcome of symptomatic progression are presented in Table 1. Where necessary, calculations conducted by the Institute supplement the data from the dossier and the data subsequently submitted by the company in the comments and after the oral hearing.

Kaplan-Meier curves on the event time analyses are presented in Appendix A.

Table 1: Results (mortality) – RCT, direct comparison: niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P (multipage table)

Study **outcome category** **outcome**	**Niraparib + abiraterone acetate + P**		**Placebo + abiraterone acetate + P**		**Niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P**
	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]**
MAGNITUDE					
Morbidity					
Symptomatic progression[b]	92	NA [36.5; NC] 25 (27.2[c])	88	28.3 [18.4; NC] 41 (46.6[c])	0.48 [0.29; 0.79]; 0.004[d]
Occurrence of cancer-related morbid events[e]	92	NA 5 (5.4[c])	88	NA 7 (8.0[c])	0.64 [0.20; 2.01]; 0.441[d]
External radiotherapy for skeletal events	92	NA 12 (13.0)	88	NA 18 (20.5)	0.53 [0.25; 1.10]; 0.083
Tumour-related orthopaedic-surgical intervention	92	NA 0 (0)	88	NA 1 (1.1)	NC; 0.238
Initiation of a new systemic anti-cancer therapy because of cancer pain	92	NA 9 (9.8)	88	NA [35.8; NC] 26 (29.5)	0.28 [0.13; 0.59]; < 0.001
Use of other cancer-related procedures	92	NA 5 (5.4)	88	NA 6 (6.8)	0.76 [0.23; 2.50]; 0.652
Symptomatic progression (incl. the component of chronic opioid use, presented as supplementary information)[e, f, g]	*92*	*NA [36.2; NC]* *28 (30.4[c])*	*88*	*21.7 [17.3; 35.8]* *46 (52.3[c])*	*0.46 [0.29; 0.75]; 0.002[d]*
Chronic opioid use	*92*	*NA* *6 (6.5)*	*88*	*NA* *7 (8.0)*	*0.72 [0.24; 2.15]; 0.555*

Table 1: Results (mortality) – RCT, direct comparison: niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P (multipage table)

Study outcome category outcome	Niraparib + abiraterone acetate + P		Placebo + abiraterone acetate + P		Niraparib + abiraterone acetate + P vs. placebo + abiraterone acetate + P
	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]

a. HR, 95% CI calculated using unstratified Cox proportional hazards model; p-value calculated using an unstratified log-rank test.
b. Number of patients with qualifying event for the composite outcome of symptomatic progression (intervention vs. control arm):
- Component "occurrence of cancer-related morbidity events": 4 (4%) vs. 6 (7%).
- Component "external radiotherapy for skeletal symptoms": 10 (11%) vs. 16 (18%).
- Component "tumour-related orthopaedic surgical intervention": 0 vs. 0.
- Component “initiation of a new systemic anti-cancer therapy because of cancer pain”: 7 (8%) vs. 17 (19%).
- Component "Use of other cancer-related procedures": 4 (4%) vs. 3 (3%).

c. Institute’s calculation.
d. HR, 95 % CI, and p-value calculated using an unstratified Cox proportional hazards model.
e. Only the following cancer-related morbid events are included in the analyses subsequently submitted by the company with the comments: spinal cord compression and fractures (symptomatic and/or pathological).
f. Sensitivity analysis with addition of the component “time to chronic opioid use” (defined by the company as oral opioid consumption for ≥ 3 weeks; parenteral opioid consumption for ≥ 7 days) within the outcome “time to symptomatic progression”.
g. Information on the number of patients with a qualifying event is missing.

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; P: prednisone or prednisolone; RCT: randomized controlled trial

A statistically significant difference in favour of niraparib + abiraterone acetate + P was shown for the outcome of symptomatic progression. This yields a hint of an added benefit of niraparib + abiraterone acetate + P compared to abiraterone acetate + P. The extent of the added benefit for this outcome cannot be quantified due to the uncertainties described in Section 2.1 (text section "Summary and consequences for the extent of the added benefit").

Subgroups and other effect modifications

Analogue to dossier assessment A23-107, the following subgroup characteristics were considered:

- age (< 65 years/≥ 65 years to < 75 years/≥ 75 years)
- prior taxane-containing chemotherapy (yes/no)

Regarding the outcome of symptomatic progression, there was no statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05).

2.1.3 Overall conclusion on added benefit

Table 2 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 2: Positive and negative effects from the assessment of niraparib/abiraterone acetate + P in comparison with abiraterone acetate + P

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
Mortality ▪ overall survival ▫ prior taxane-containing chemotherapy (no): hint of an added benefit – extent: “major”	–
Serious/severe symptoms/late complications ▪ symptomatic progression: hint of added benefit – extent: "non-quantifiable"	–
Outcomes with shortened observation period	
–	Serious/severe side effects ▪ Anaemia (severe AEs): hint of greater harm – extent “major”
AE: adverse event	

In comparison with benefit assessment A23-107, an additional positive effect was shown for the outcome of symptomatic progression for all patients in research question 1.

Due to the existing effect modification for the characteristic “prior taxane-containing chemotherapy” for the outcome of overall survival, the results on the added benefit of niraparib/abiraterone acetate + P versus the ACT after prior taxane-containing chemotherapy are derived separately below:

Patients without prior taxane-containing chemotherapy

For patients without prior taxane-containing chemotherapy, there was a hint of major added benefit for the outcome of overall survival, and for the outcome of symptomatic progression in the outcome category serious/severe symptoms/consequential complications there was hint of non-quantifiable added benefit. On the other hand, there is a hint of greater harm with major extent for the outcome of anaemia in the outcome category of serious/severe side

effects. In the weighing of benefit versus harm, this resulted in a downgrading of the extent of the added benefit. Overall, there is therefore a hint of considerable added benefit for patients without prior taxane-containing chemotherapy.

Patients with prior taxane-containing chemotherapy

For patients with prior taxane-containing chemotherapy, there was no hint of added benefit for the outcome of overall survival, but for the outcome of symptomatic progression there was a hint of non-quantifiable added benefit. On the other hand, there is a hint of greater harm with major extent for the outcome of anaemia in the outcome category of serious/severe side effects. Overall, there was a hint of a minor added benefit for patients with prior taxane-containing chemotherapy.

Summary

In summary, there was a hint of considerable added benefit of niraparib/abiraterone acetate + P versus abiraterone acetate + P for patients without prior taxane-containing chemotherapy with treatment-naive mCRPC and BRCA1/2 mutations for whom chemotherapy is not clinically indicated. For patients with prior taxane-containing chemotherapy, there was a hint of minor added benefit compared to abiraterone acetate + P.

2.2 Summary

The data subsequently submitted by the company in the commenting procedure changed the conclusion on the added benefit of niraparib/abiraterone acetate + P from dossier assessment A23-107 [1] for research question 1: For the subgroup of adults with prior taxane-containing chemotherapy with treatment-naive mCRPC and BRCA1/2 mutation in whom chemotherapy is not clinically indicated, there was a hint of minor added benefit of niraparib/abiraterone acetate + P compared with the ACT. As with research question 2, there were no changes compared to dossier assessment A23-107 for the subgroup of adults without prior taxane-containing chemotherapy of research question 1.

The following Table 3 shows the result of the benefit assessment of niraparib/abiraterone acetate + P under consideration of dossier assessment A23-107 and the present addendum.

Table 3: Niraparib/abiraterone acetate – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with treatment-naive mCRPC and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated[b, c, d]	▪ **Abiraterone acetate in combination with prednisone or prednisolone** (only for patients whose disease is progressive during or after docetaxel-containing chemotherapy; only for patients with asymptomatic or mildly symptomatic disease after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated), or ▪ enzalutamide (only for patients whose disease has progressed during or after docetaxel chemotherapy; only for patients with asymptomatic or mildly symptomatic disease after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated), or ▪ olaparib as monotherapy (only for patients whose disease has progressed after previous treatment that included an NHA), or ▪ olaparib in combination with abiraterone acetate and prednisone or prednisolone	▪ Patients without prior taxane-containing chemotherapy: hint of considerable added benefit[e] ▪ patients with prior taxane-containing chemotherapy: hint of minor added benefit[e]
2	Adults with pretreated mCRPC and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated[b, f]	Individualized treatment[g] selected from ▪ abiraterone acetate in combination with prednisone or prednisolone (only for patients whose disease has progressed on or after docetaxel-containing chemotherapy), ▪ enzalutamide (only for patients whose disease has progressed on or after docetaxel chemotherapy) ▪ olaparib as monotherapy (only for patients whose disease has progressed after previous treatment that included an NHA), taking into accounts any pretreatment(s).	Added benefit not proven

Table 3: Niraparib/abiraterone acetate – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
a. Presented is the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. For the present therapeutic indication, it is assumed according to the G-BA that an existing conventional ADT is continued. In the context of the present therapeutic indication, conventional ADT means surgical castration or medical castration using treatment with GnRH agonists or antagonists. c. The ACT specified here comprises several alternative treatment options according to the G-BA. However, the treatment options only represent a comparator therapy for those members of the patient population who have the patient and disease characteristics shown in brackets. The alternative treatment options are only to be regarded as equally appropriate in the area in which the patient populations have the same characteristics. The sole comparison with a therapy option which represents a comparator therapy only for part of the patient population is generally insufficient to demonstrate added benefit for the overall population. d. When determining the ACT, it is assumed that the patients may have already received prior therapy with docetaxel or NHA in earlier stages of the disease. e. Only patients with ECOG PS of 0 or 1 and a BPI-SF Item 3 ≤ 3 (mildly symptomatic or asymptomatic) were included in the MAGNITUDE study. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or to patients who were symptomatic at baseline (BPI-SF Item 3 > 3) (see also FN c, on the G-BA's notes on the ACT). f. When determining the ACT, it is assumed that the patients, in addition to prior therapy of the mCRPC, may have already received prior therapy with docetaxel or NHA in earlier stages of the disease. g. For the implementation of individualized therapy in a study of direct comparison, according to the G-BA, investigators are expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; BRCA: breast cancer susceptibility gene; FN: footnote; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; mCRPC: metastatic castration resistant prostate cancer; NHA: new hormonal agent; P: prednisone or prednisolone			

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.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Niraparib/Abirateronacetat (Prostatakarzinom); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2024 [Accessed: 28.03.2024]. URL: https://dx.doi.org/10.60584/A23-107.

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Appendix A Kaplan-Meier curves on the time-to-event analyses presented in the addendum (research question 1: adults with treatment-naive mCRPC and BRCA1/2 mutation in whom chemotherapy is not clinically indicated)

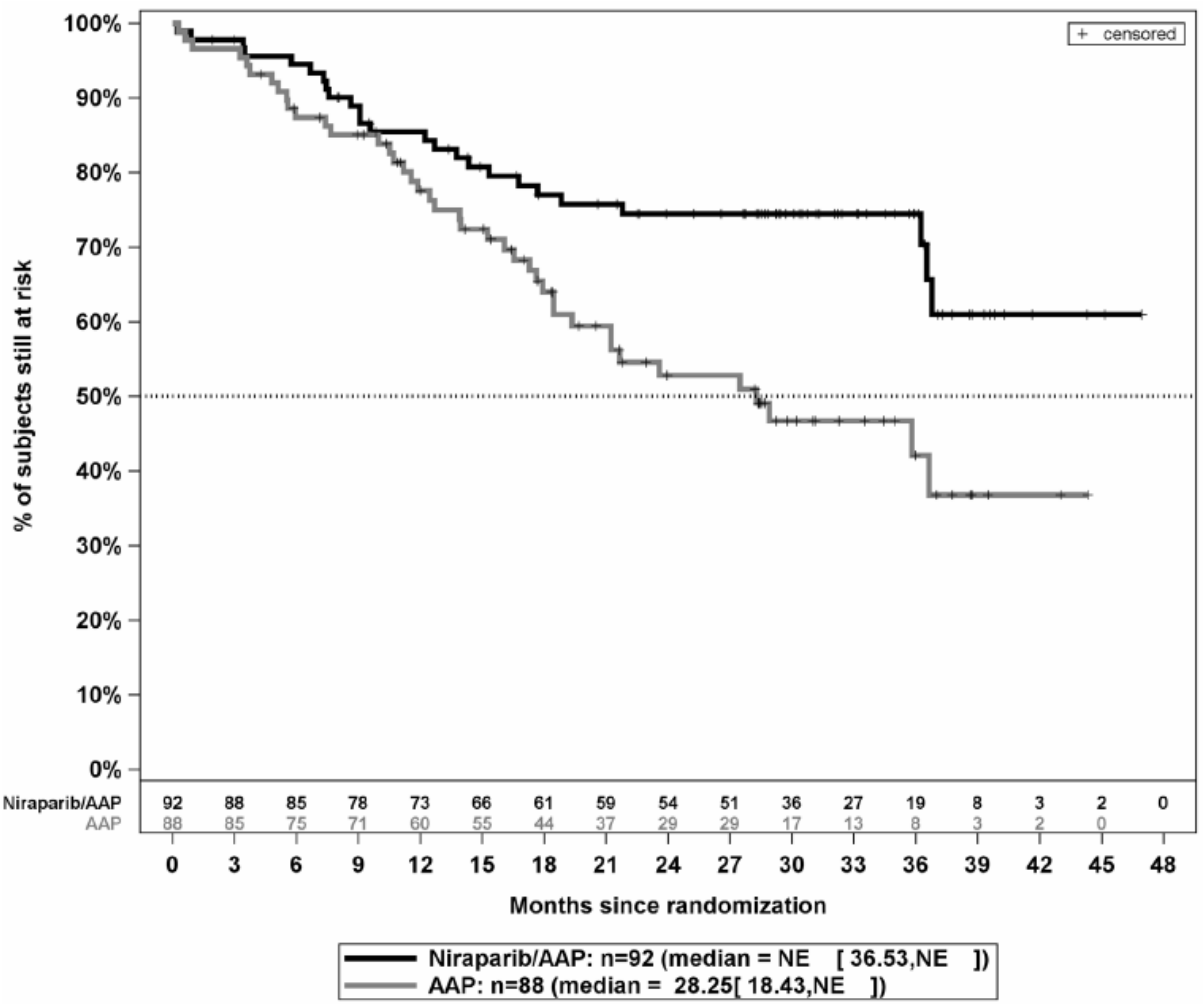

Figure 1: Kaplan-Meier curves for the outcome of symptomatic progression, MAGNITUDE study

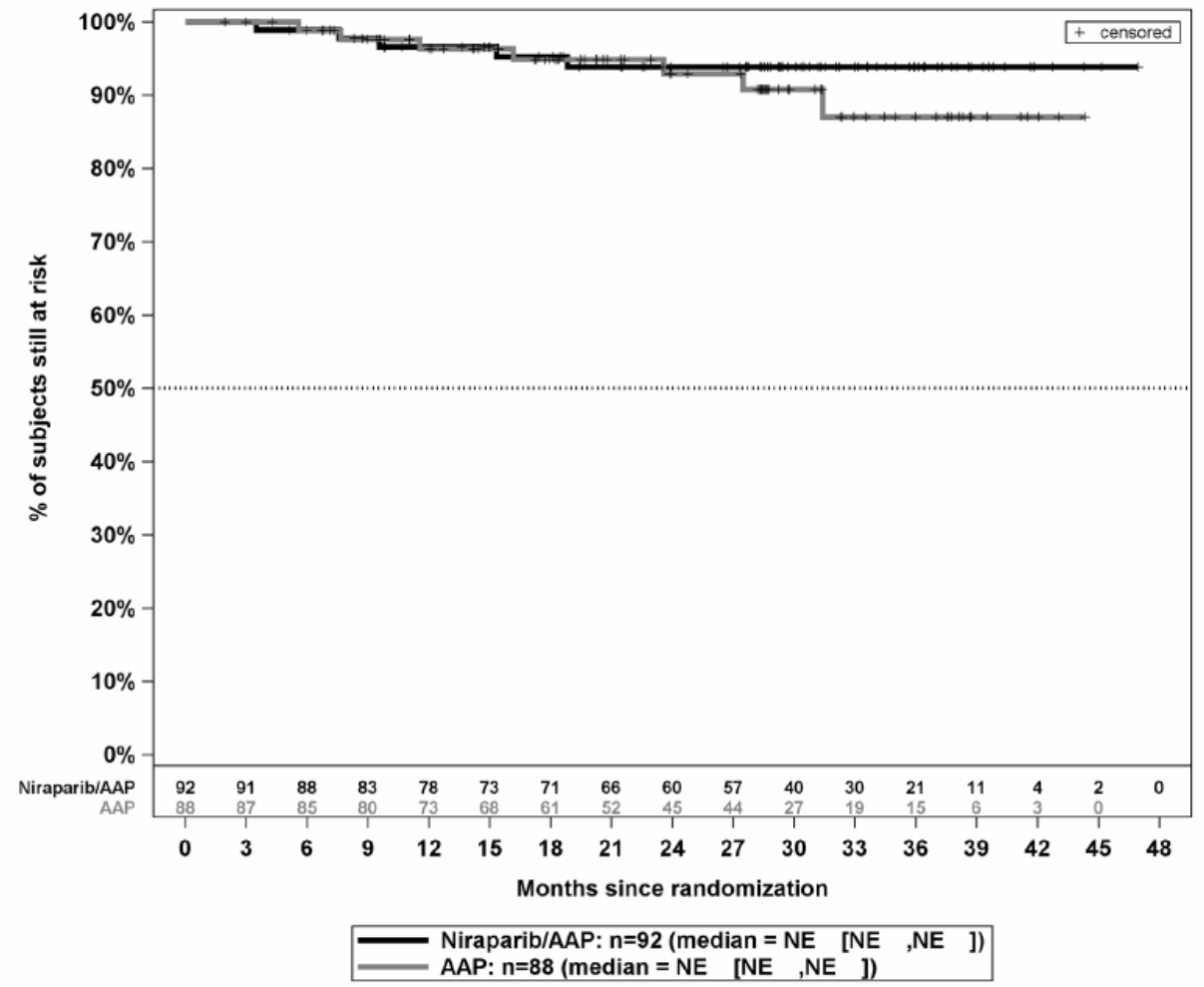

Figure 2: Kaplan-Meier curves for the component "occurrence of cancer-related morbid events" of the outcome “symptomatic progression”, MAGNITUDE study

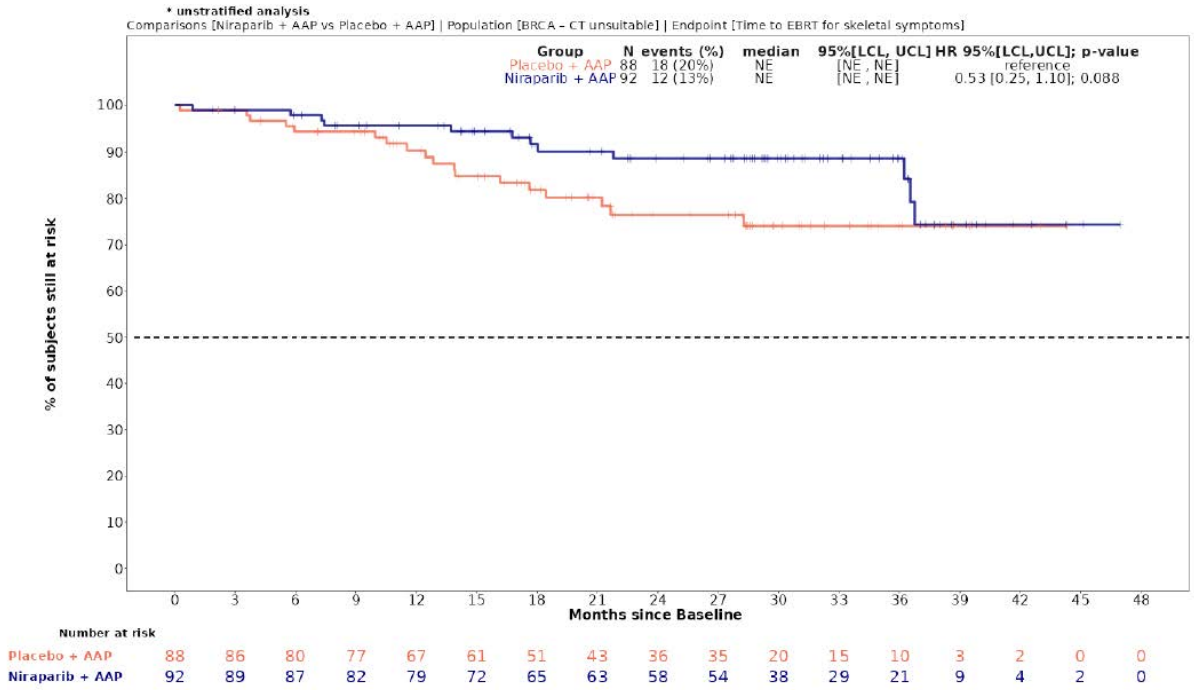

Figure 3: Kaplan-Meier curves for the component "external radiotherapy for skeletal symptoms" of the outcome “symptomatic progression”, MAGNITUDE study

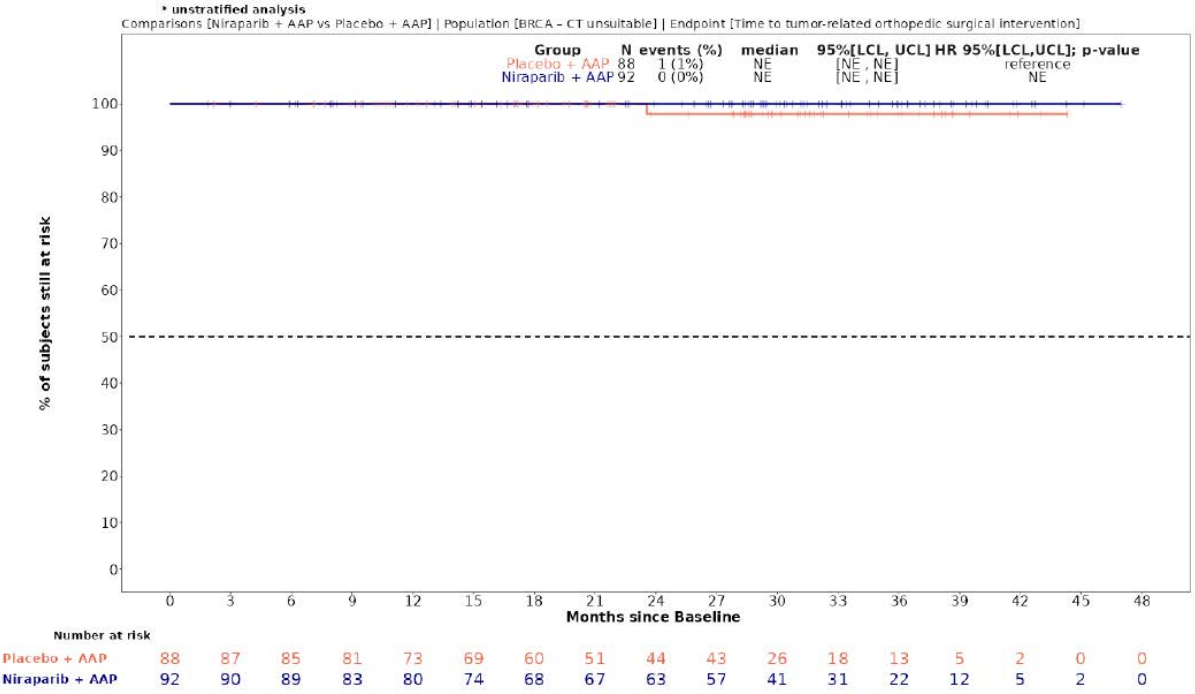

Figure 4: Kaplan-Meier curves for the component "tumour-related orthopaedic surgical intervention” of the outcome “symptomatic progression”, MAGNITUDE study

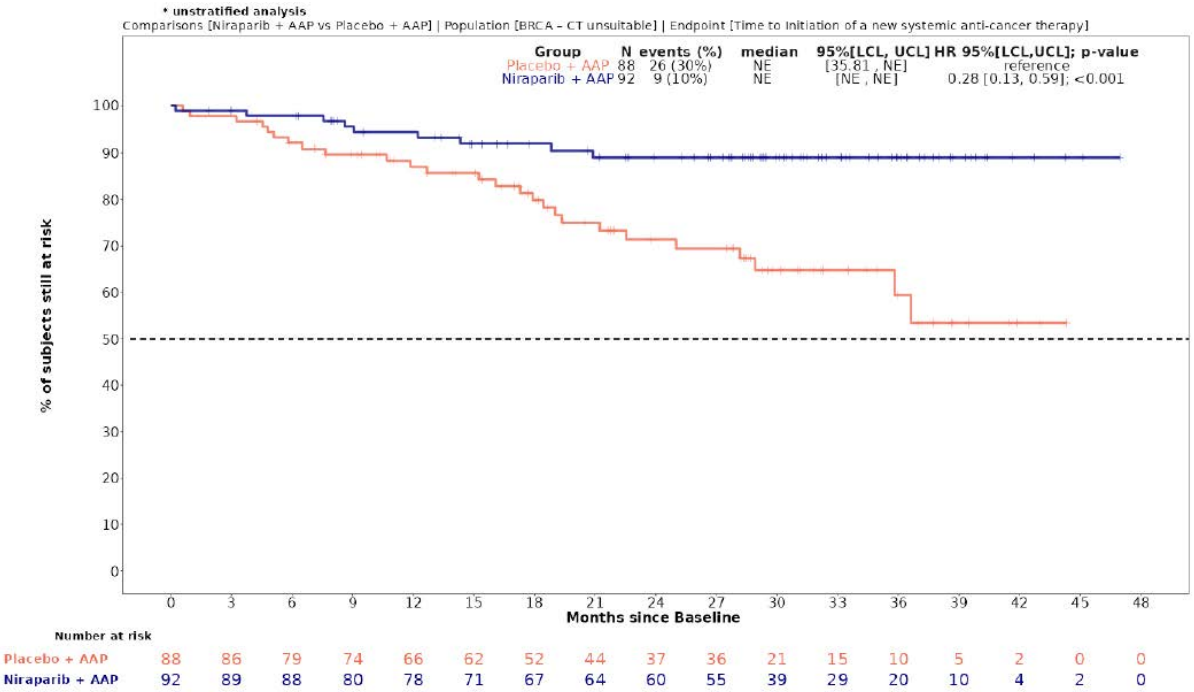

Figure 5: Kaplan-Meier curves for the component "initiation of a new systemic anti-cancer therapy because of cancer pain" of the outcome “symptomatic progression”, MAGNITUDE study

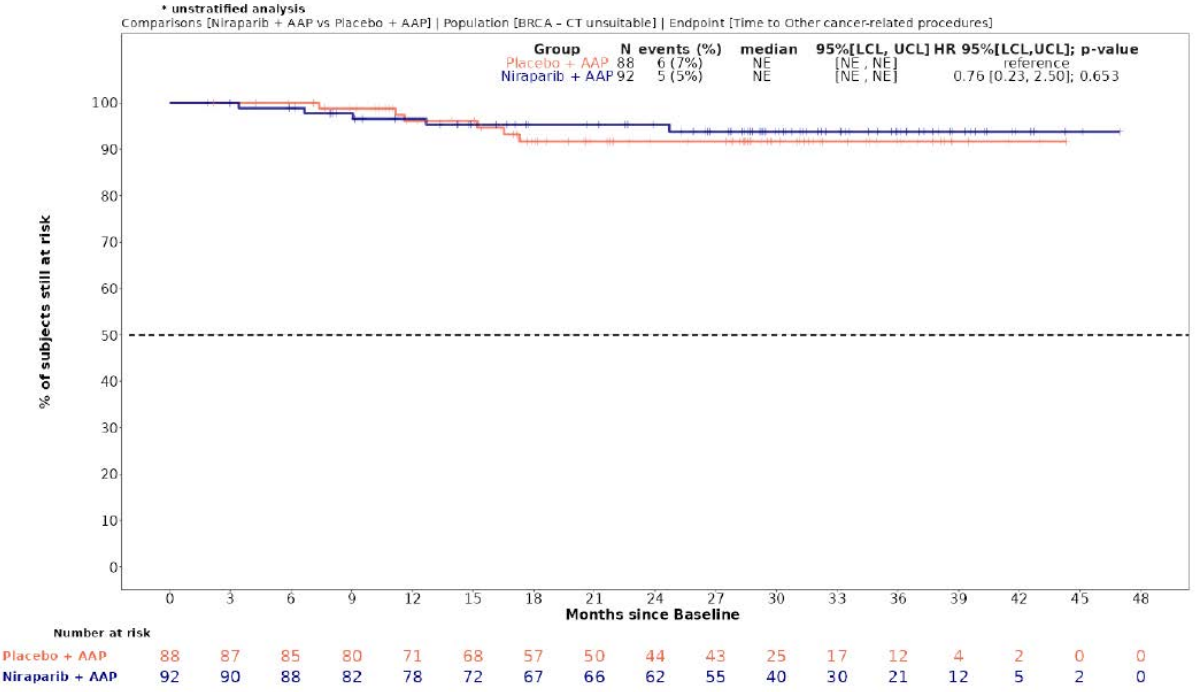

Figure 6: Kaplan-Meier curves for the component "use of other cancer-related procedures" of the outcome “symptomatic progression”, MAGNITUDE study

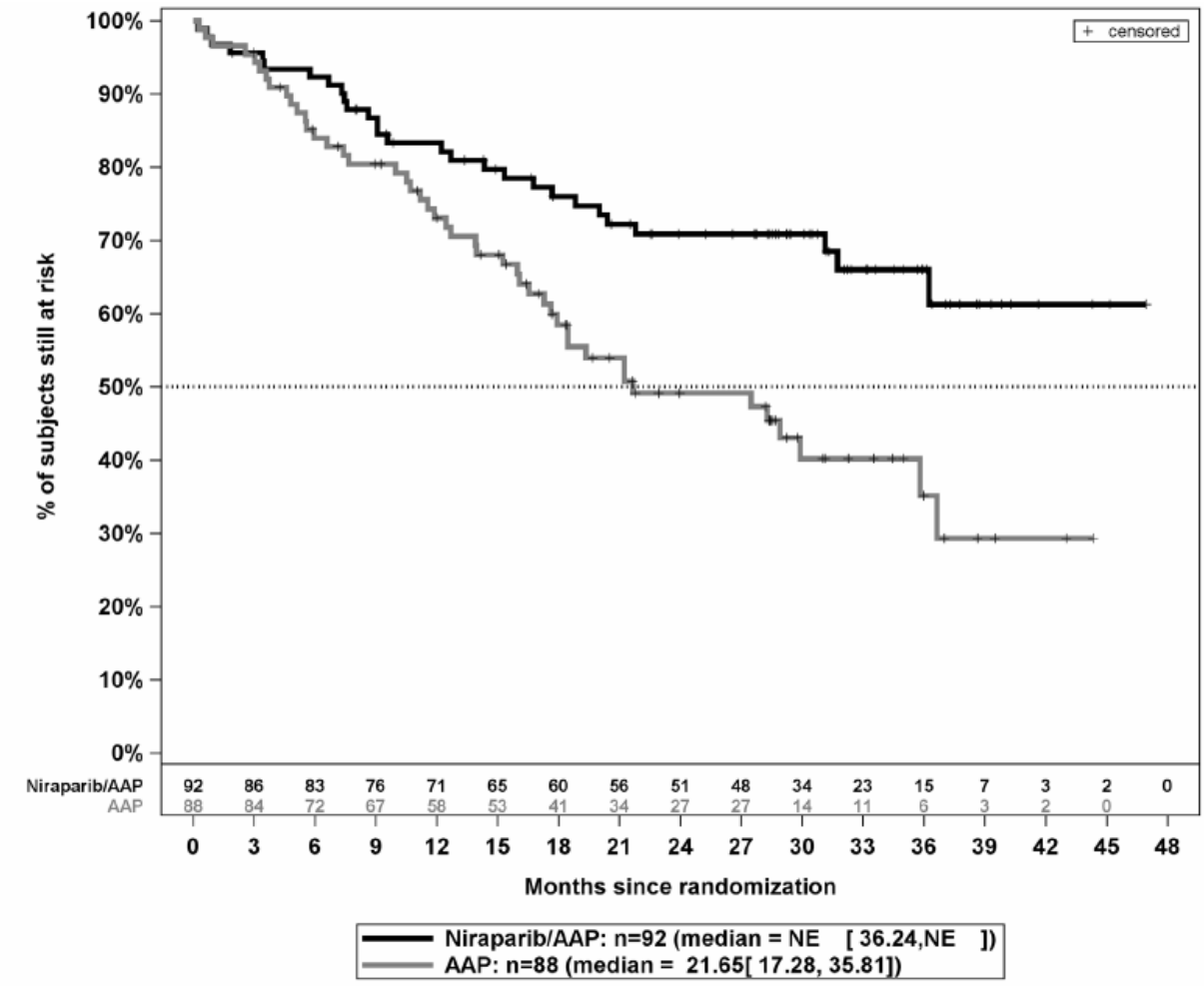

Figure 7: Kaplan-Meier curves for the outcome “symptomatic progression (including the component "chronic opioid use"), sensitivity analysis, MAGNITUDE study