Olaparib
(breast cancer, adjuvant)

Addendum to Project A22-89
(dossier assessment)[1]

ADDENDUM

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AML	acute myeloid leukaemia
CSR	clinical study report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
RCT	Randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized MedDRA Query
SOC	System Organ Class

1 Background

On 10 January 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments on Commission A22-89 (Olaparib – Benefit assessment according to § 35a Social Code Book V) [1].

The commission comprises the assessment of the sensitivity analyses on serious adverse events (SAEs) without consideration of the System Organ Class (SOC) of neoplasms benign, malignant and unspecified (incl cysts and polyps) subsequently submitted by the pharmaceutical company (hereinafter referred to as the "company") in the commenting procedure [2], as well as the assessment of the analyses for the specific adverse events (AEs) (myelodysplastic syndrome [MDS] and acute myeloid leukaemia [AML] as well as pneumonitis) with follow-up periods until the end of the study or death, in each case taking into account the information in the dossier [3].

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

The randomized controlled trial (RCT) OlympiA was used for the benefit assessment of olaparib. A detailed description of the study can be found in dossier assessment A22-89 [1].

In accordance with the commission, the analyses on the outcomes of SAEs and specific AEs subsequently submitted by the company in the commenting procedure are assessed below.

2.1 Analyses on side effects

SAEs

As described in benefit assessment A22-89, the analyses presented by the company in the dossier for the outcome of SAEs are not suitable for the benefit assessment, as the analysis included a relevant percentage of progression events from the SOC of neoplasms benign, malignant and unspecified (including cysts and polyps). In the commenting procedure, the company presented an analysis for the outcome of SAEs without consideration of the SOC of neoplasms benign, malignant and unspecified (incl cysts and polyps). This analysis is used for the benefit assessment.

Specific AEs

The composite outcome of MDS and AML (standardized Medical Dictionary for Regulatory Activities [MedDRA] Query [SMQ] + Preferred Term [PT] list, AE) and the outcome of pneumonitis (SMQ, AE) were used for benefit assessment A22-89. According to the study protocol, these outcomes were to be observed until study end or death. However, the analyses of these outcomes presented in the company's dossier only covered the treatment period plus 30 days. These analyses were nevertheless used for the benefit assessment in the present data situation, as it was clear from the clinical study report (CSR) that there were no additional events of relevant extent for these outcomes in the period after the end of treatment (see dossier assessment A22-89). In the commenting procedure, the company now presented analyses with a follow-up duration until study end or death. In principle, these analyses are to be preferred for the benefit assessment, as they have a higher information content.

2.1.1 Risk of bias

The risk of bias of results for all outcomes in the side effects category is rated as low.

2.1.2 Results

The results for the outcome of SAEs without consideration of the SOC of neoplasms benign, malignant and unspecified (incl cysts and polyps) as well as for the specific AEs of MDS and AML (SMQ + PT list, AEs) and pneumonitis (SMQ, AEs) from the OlympiA study are shown in Table 1.

Table 1: Results (side effects, dichotomous) – RCT, direct comparison: olaparib versus placebo

Study Outcome category Outcome	Olaparib N	Olaparib Patients with event n (%)	Placebo N	Placebo Patients with event n (%)	Olaparib vs. placebo RR [95% CI]; p-value[a]
OlympiA					
Side effects					
SAEs[b]	911	75 (8.2)	904	58 (6.4)	1.28 [0.92; 1.79]; 0.147
MDS and AML (SMQ + PT list, AEs)[c, d]	911	2 (0.2)	904	2 (0.2)	0.99 [0.14; 7.03]; > 0.999
Pneumonitis (SMQ, AEs)[c, d]	911	9 (1.0)	904	12 (1.3)	0.74 [0.32; 1.76]; 0.533

a. Institute's calculation of RR, 95% CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [4]).
b. Without consideration of the SOC of neoplasms benign, malignant and unspecified (including cysts and polyps).
c. Predefined in the study as AESIs.
d. Observation period until death or end of study.

AE: adverse event; AESI: adverse event of special interest; AML: acute myeloid leukaemia; CI: confidence interval; CSZ: convexity, symmetry, z-score; MDS: myelodysplastic syndrome; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: Standard MedDRA Query; SOC: System Organ Class

Side effects

SAEs (without consideration of the SOC of neoplasms benign, malignant and unspecified [incl cysts and polyps])

No statistically significant difference between treatment groups was shown for the outcome of SAEs (without consideration of the SOC of neoplasms benign, malignant and unspecified [incl cysts and polyps]). There is no hint of greater or lesser harm from olaparib in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Specific AEs

MDS and AML (SMQ + PT list, AEs)

No statistically significant difference between treatment groups was shown for the outcome of MDS and AML (SMQ + PT list, AEs). There is no hint of greater or lesser harm from olaparib in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Pneumonitis (SMQ, AE)

For the outcome of pneumonitis (SMQ, AEs), there was no statistically significant difference between treatment groups. This results in no hint of greater or lesser harm from olaparib in comparison with watchful waiting; greater or lesser harm is therefore not proven.

Consistent with the assessment in benefit assessment A22-89, the subsequently submitted analyses up to the end of the study or death therefore show no relevant differences in comparison with the analyses up to the end of treatment plus 30 days already used in the benefit assessment. Therefore, no consequence for the benefit assessment results from the subsequently submitted analyses on specific AEs.

Subgroups and effect modifiers

The company presented no subgroup analyses for the subsequently submitted analyses on the outcome of SAEs without consideration of the SOC of neoplasms benign, malignant and unspecified (incl cysts and polyps), on the specific AEs of MDS and AML (SMQ + PT list, AE) as well as pneumonitis (SMQ, AE) with follow-up periods until death or end of study.

Conclusions on a possible effect modification by the characteristic of age are therefore not possible for the outcome of SAEs. For the specific AEs of MDS and AML (SMQ + PT list, AE) as well as pneumonitis (SMQ, AE) with a follow-up period until death or end of study, there are only minor deviations from the analyses already used in the benefit assessment. For these outcomes, it is therefore not assumed that the results from subgroup analyses on the subsequently submitted analyses would show a relevant difference compared with the subgroup analyses available in the dossier on the analyses up to the end of treatment plus 30 days.

2.1.3 Probability and extent of added benefit

2.1.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.1.2. Table 2 presents only the relevant results in the present addendum.

Table 2: Extent of added benefit at outcome level: olaparib versus watchful waiting

Outcome category **Outcome**	**Olaparib vs. placebo** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Shortened observation period		
Side effects		
SAEs	8.2% vs. 6.4% RR: 1.28 [0.92; 1.79] p = 0.147	Greater/lesser harm not proven
Total observation period		
Side effects		
MDS and AML (AEs)	0.2% vs. 0.2% RR: 0.99 [0.14; 7.03] p > 0.999	Greater/lesser harm not proven
Pneumonitis (AEs)	1.0% vs. 1.3% RR: 0.74 [0.32; 1.76] p = 0.533	Greater/lesser harm not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size and the scale of the outcome are made with different limits based on the upper or lower limit of the confidence interval (CI_u or CI_L).

AE: adverse event; AML: acute myeloid leukaemia; CI: confidence interval; CI_L: lower limit of confidence interval; CI_u: upper limit of confidence interval; MDS: myelodysplastic syndrome; RR: relative risk; SAE: serious adverse event

2.1.3.2 Overall conclusion on added benefit

Table 3 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 3: Positive and negative effects from the assessment of olaparib in comparison with watchful waiting

Positive effects	Negative effects
Total observation period	
Mortality ▪ Overall survival: indication of an added benefit – extent: considerable	–
Morbidity Serious/severe symptoms / late complications ▪ Recurrences: indication of an added benefit – extent: considerable	–
Shortened observation period	
–	Morbidity Non-serious/non-severe symptoms / late complications ▪ Nausea and vomiting (symptoms, EORTC QLQ-C30): hint of lesser benefit – extent: minor
–	Serious/severe side effects ▪ Severe AEs: indication of greater harm – extent: major ▫ Investigations (severe AEs): indication of greater harm – extent: major ▪ Anaemia (SAEs): indication of greater harm – extent considerable
–	Non-serious/non-severe side effects ▪ Discontinuation due to AEs: indication of greater harm – extent: considerable ▪ Fatigue (AEs), gastrointestinal disorders (AEs), dysgeusia (AEs), appetite decreased (AEs): each hint of greater harm – extent: considerable
AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire – Core 30; SAE: serious adverse event	

Compared with dossier assessment A22-89, usable results are now available for the outcome of SAEs. No positive or negative effect in comparison with the appropriate comparator therapy (ACT) was found for this outcome. Overall, the present addendum therefore does not result in any further positive or negative effects.

2.2 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of olaparib from dossier assessment A22-89. The following Table 4 shows the result of the benefit assessment of olaparib under consideration of dossier assessment A22-89 and the present addendum.

Table 4: Olaparib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with germline BRCA-mutant, HER2-negative, high recurrence-risk early breast cancer; after neoadjuvant or adjuvant chemotherapy[b]; adjuvant treatment	Watchful waiting[c]	Indication of minor added benefit

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, (neo)adjuvant chemotherapy and surgery are assumed to have been completed.
c. Adjuvant radiotherapy may be performed sequentially or in parallel with endocrine therapy. According to the G-BA, adjuvant radiotherapy is not part of the ACT.

ACT: appropriate comparator therapy; BRCA: breast cancer gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2

The G-BA decides on the added benefit.

3 References

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